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News & Features FROM NIH

January 1980

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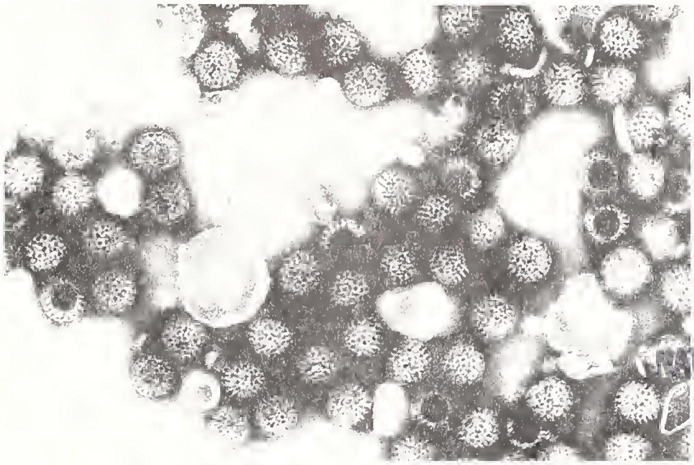

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INFANTILE DIARRHEA VIRUS GROWN: VACCINE IS FORESEEN

An important step toward developing a vaccine to prevent a serious diarrheal disease in infants has been reported by scientists from NIH's National Institute of Allergy and Infectious Diseases (NIAID).

This NIAID effort, headed by Dr. Richard G. Wyatt, has succeeded in efficiently growing a virus identified as a major cause of serious diarrhea in infants and young children throughout the world. The accomplishment will enable the investigators to study the connection between the virus's genetic structure and its ability to cause disease. Armed with this information, they may then be able to create a weakened virus that could be used as an effective vaccine.

The virus, known as the rotavirus, was first identified in 1973 by Australian scientists, who examined specimens from young patients stricken with severe diarrhea. Since then, epidemiologic studies from many parts of the world, including the United States, have revealed that rotaviral infection is responsible for approximately 50 percent of serious diarrheal diseases in hospitalized infants and young children.

Diarrhea, A Leading Cause of Infant Deaths

Diarrheal diseases are a leading cause of death among the very young in many of the developing countries. For instance, in 1975, diarrhea was estimated to have caused between five and 18 million deaths worldwide in children under five years of age.

In commenting on the impact of diarrheal diseases, NIAID Director Dr. Richard M. Krause said, "Although the proportion of deaths due to rotavirus is not currently known, it is suspected that this virus accounts for a large

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share of mortality associated with diarrhea. Since diarrhea can be so devastating in the younger age group, a rotavirus vaccine is urgently needed."

Strategy Used to Grow Virus

Previous laboratory attempts at growing human rotavirus in sufficient quantities for vaccine development have failed. However, in the reported study, the NIAID team succeeded in growing a strain of the virus efficiently in monkey kidney cells--laboratory-grown cells widely used in reproducing virus for investigation and for vaccines. The strain of rotavirus used--type 2--was preselected from one of 42 stool specimens obtained mostly from young patients with serious diarrhea at Children's Hospital in Washington, D.C. This strain was chosen because of its ability to initiate the early stages of infection in monkey kidney cells. Among the rotaviruses, type 2 is the most prevalent cause of serious diarrheal disease.

The type 2 rotavirus strain, as recovered from the patient, could not be propagated (grown) serially in tissue cultures of monkey kidney cells. For this reason, the investigators selected a susceptible animal--in this case, the newborn germfree piglet--in which the virus did grow well. By passing the virus from piglet to piglet, they increased the probability that an altered virus (mutant) capable of growing in tissue culture would emerge. After 11 successive passages from piglet to piglet, the desired virus was detected and could be transferred from the piglets to monkey cells in culture. Previous attempts to transfer the virus from human specimens or from earlier passages in the piglets failed to yield virus that grew efficiently in cultured cells.

The tissue culture-adapted virus was then passaged 14 times in monkey cells, demonstrating its ability for continuous growth in culture. Various laboratory tests confirmed the identity of the tissue culture-adapted virus

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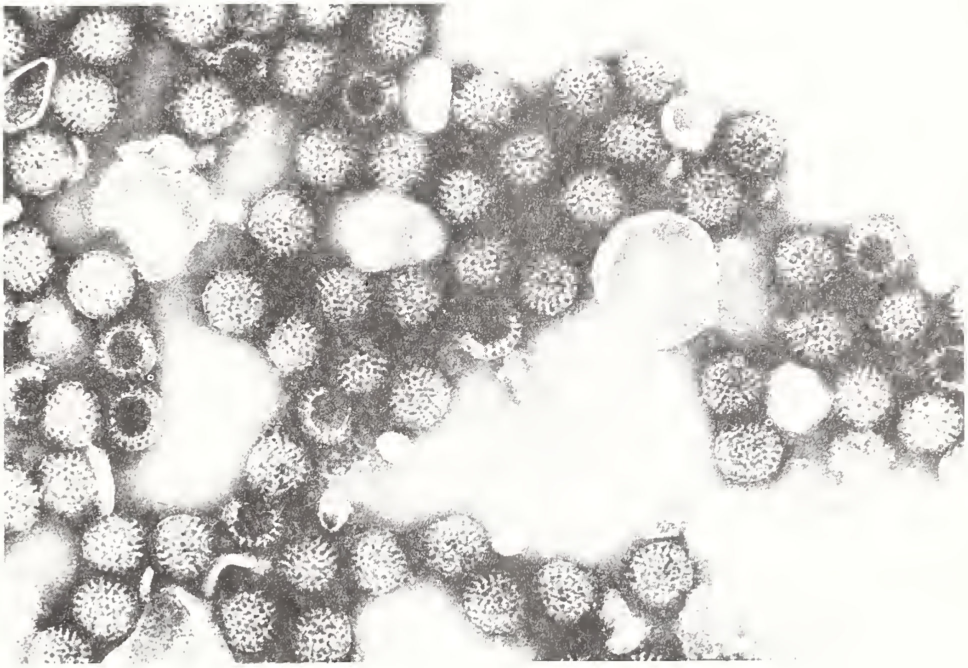
as the strain originally obtained from the patient.

This research was reported in the January 11 issue of *Science* by Richard G. Wyatt, M.D., Walter D. James, Anthony R. Kalica, Ph.D., Harry B. Greenberg, M.D., Albert Z. Kapikian, M.D., and Robert M. Chanock, M.D., all of the Laboratory of Infectious Diseases, NIAID; and Edward H. Bohl, D.V.M., Ph.D., Kenneth W. Theil, Ph.D., and Linda J. Saif, Ph.D., all of Ohio Agricultural Research and Development Center, Wooster, Ohio.



The photo above is an electron micrograph of human rotavirus in a fecal specimen magnified 224,840 times. NIH's NIAID scientists have succeeded in growing the virus which has been identified as a major cause of perirus diarrhea in infants and young children throughout the world. This accomplishment may be an important step toward developing a vaccine to prevent serious diarrheal diseases. (NIH Photo #1630)

# # #

MILD HYPERTENSION CONTROL LOWERS MORTALITY

The results of a 5-year clinical study on blood pressure control indicate that health benefits from adequate blood pressure control extend to subjects with mild hypertension as well as to those with high blood pressure.

NIH's National Heart, Lung, and Blood Institute-supported Hypertension Detection and Follow-up Program (HDFP) found evidence, in earlier clinical trials, that blood pressure control in patients with moderate to severe hypertension (diastolic blood pressures of 105 mm/hq or higher), substantially reduced the threat of such associated disorders as stroke, congestive heart failure, and renal failure.

The study involved 14 clinical centers, four coordination and service centers, and nearly 11,000 subjects, most of them with mild hypertension.

Half of the subjects were referred to their usual sources of medical care and were seen by HDFP annually. The other half participated in a stepped-care program of therapy at HDFP Centers and were seen every 4 months, or more often if necessary. All subjects were followed for 5 years.

Goal blood pressure levels were set for every study participant. For those patients with diastolic pressures of 100 or greater or who were already on antihypertensive medication at entry, the goal was a reduction to 90 mm/hq. For those with diastolic pressures of 90-99 at entry, the goal was a reduction of 10 mm/hq.

Not all patients in the stepped-care group required medication. If their blood pressures were at or below the set goal at the first treatment visit and not already on medication, the patients did not receive a prescription. They

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were then designated as step 0 unless or until their blood pressure status changed for the worse.

For stepped-care patients requiring medication, a systematic, standardized program of anti-hypertensive therapy was employed. Medications were added or dosages adjusted as needed in stepwise fashion to bring each patient to or below his goal blood pressure.

At step 1, the diuretic chlorthalidone was prescribed. At step 2, an anti-adrenergic drug (usually reserpine) was added. At step 3, a vasodilator (usually hydralazine) was added. At step 4, a more potent anti-adrenergic drug (usually quanethidine) was added, with or without discontinuance of previously prescribed medications. By step 5, the investigators could use any FDA-approved drug or combination that seemed to work well. Most patients required only step 1 or step 2 therapy for adequate blood pressure control.

All medications were provided free to stepped-care patients and special efforts were made to encourage clinic attendance and faithful adherence to medication schedules.

Results from the 5-year period of the study indicate that blood pressure control was consistently better in the stepped-care group than in the referred-care group. By the fifth year, nearly 65 percent of the former were at or below their goal blood pressure levels (over half of them in the normotensive range), whereas only 44 percent of referred-care patients achieved their goals.

The more effective blood pressure control achieved in the stepped-care group was reflected in their lower mortality rates. Their 5-year mortality was nearly 17 percent lower for all causes of death and their mortality from cardiovascular disease was 18 percent lower.

Particularly noteworthy were the mortality reductions achieved among

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stepped-care patients with diastolic pressures of 90-104, the group for which the efficacy of treatment has been controversial. Compared with referred-care patients in the same blood-pressure stratum, the stepped-care patients experienced a 20 percent lower mortality from all causes and a 26 percent lower mortality from cardiovascular disease.

About 70 percent of the 35 million Americans with definite hypertension have blood pressure levels between 90-104. Therefore, the HDFP results emphasize the great life-saving potential of identifying all individuals with elevated blood pressure (however "mild" their hypertension).

The study findings were described in two articles in the December 7, 1979 issue of the *Journal of the American Medical Association*.

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News & Features
FROM NIH

NEW BLOOD SEPARATING TECHNIQUE PREVENTS FATAL IRON BUILDUP

Scientists at the National Institutes of Health have begun using a new blood transfusion procedure that may significantly improve the management of patients with hereditary anemias who often succumb to heart and liver problems associated with long-term multiple transfusion therapy.

Dr. Harvey G. Klein, Chief of NIH's Clinical Center Blood Bank Pheresis Unit, said the advance involves a new technique for collecting newborn red blood cells for transfusion to patients with congenital anemias such as thalassemia major and sickle cell anemia.

In the past these patients have had to suffer the life-threatening consequences associated with their long-term transfusion treatment, namely, the buildup of iron that can destroy the functioning of vital organs.

Because newborn cells, or neocytes, have a much longer life span than mature red blood cells, the number of transfusions required by patients should be cut in half, thereby reducing significantly the risk of iron buildup in their bodies.

Dr. Klein said that the buildup of iron in the anemic patients' blood is often a greater threat to their lives than the anemia itself. The buildup results when the transfused red blood cells age, die and release their iron content into the bloodstream.

The new procedure to collect neocytes, cells with an average age of 30 days, utilizes a machine called a blood cell separator. Developed jointly by NIH and the International Business Machines Corporation in the late 1960's, the machine uses centrifugal force to separate the various components of a

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donor's blood - mature red cells, white cells, platelets and now neocytes - which are all of different densities.

The components are separated by the IBM 2997 Blood Cell Separator in a "continuous flow" method. Blood is removed from one arm of the donor, circulated through the machine to remove and collect the desired component, and the balance is returned to the donor immediately through the other arm.

Prior to the new procedure, chemical agents alone were used to remove the excess iron. However, removal did not reverse the damage already done to the vital organs. After about 50 transfusions, many patients began to have liver and heart dysfunction; after several hundred transfusions, many patients died. The use of neocytes together with the chemical agents should improve the survival of persons with transfusion-dependent anemias.

NIH is treating several patients who require long-term transfusions for thalassemia major - a hereditary blood disorder that causes fatigue, weakness, stunted growth, abnormal bone development and often death. The major limitations with the new procedure are cost and the availability of donors.

NIH is also using blood cell separators in both the Blood Bank and the National Cancer Institute to collect white blood cells and platelets to help cancer patients fight infections and hemorrhaging.

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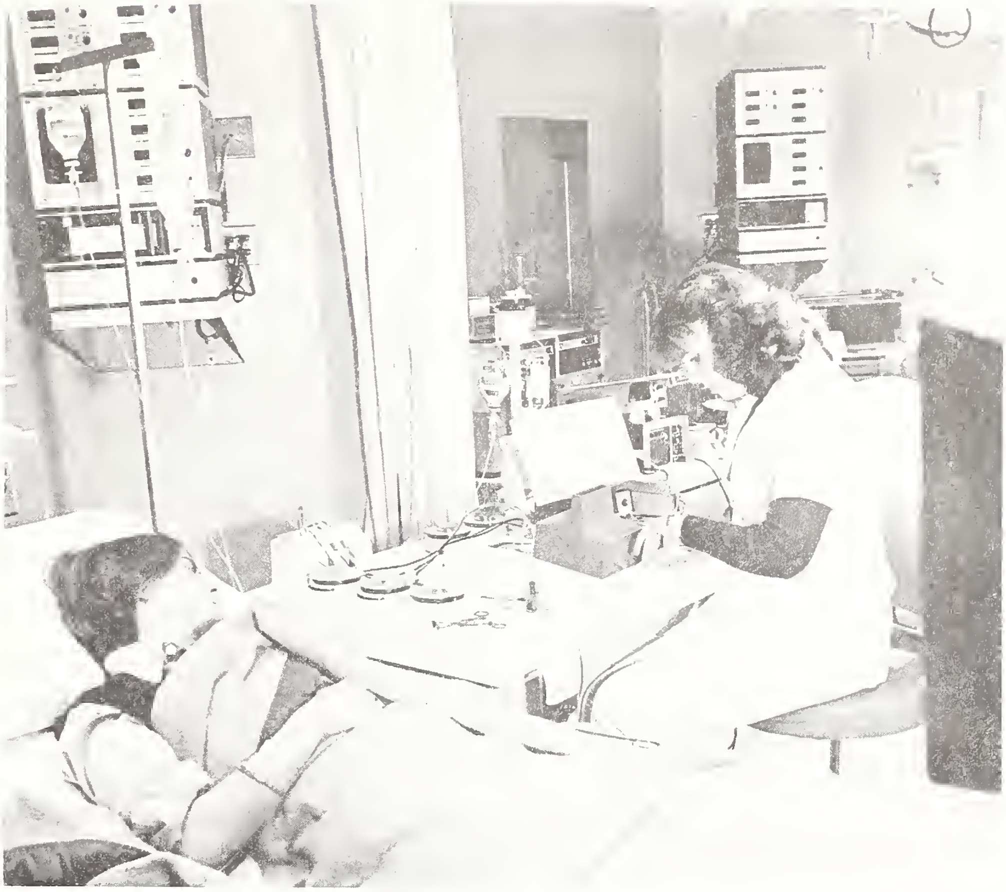

The blood cell separator uses centrifugal force to sort out the various components of a donor's blood. The new procedure which isolates neocytes should cut in half the number of transfusions necessary and therefore, hopefully improve the management of hereditary anemias. (NIH Photo #1631)

# # #

News & Features
FROM NIH

"DIABESITY" CAN BE CONTROLLED BY EXERCISE AND DIET

Most of the approximately 7 million Americans who are both obese and diabetic can control their disease by achieving weight loss through a combination of calorie and carbohydrate restriction with exercise, according to a recent report by the Division of Research Resources of the National Institutes of Health. The associated symptoms of adult-onset obesity and adult-onset diabetes have been labeled "diabesity" by Dr. E. A. H. Sims, head of a team of researchers at the University of Vermont College of Medicine.

"I don't suggest diabesity is a single disease entity," he said. "There are several obesity syndromes, and there are certainly also several subtypes of diabetes. There tends to be, however, a cluster of characteristics we call diabesity that can be distinguished from insulin dependent diabetes or childhood onset obesity. It is a progressive disorder in adults."

The researcher maintains that "diabesity" is also strongly associated with hypertension, blood lipid abnormalities, and blood vessel diseases. The obesity is more central rather than uniformly distributed as it is in lifelong obesity. "Unlike insulin-dependent diabetics, these are not truly dependent on exogenous insulin. At least in the early stages of the disorder, the pancreas may produce more than normal amounts of insulin, but not enough to meet the demand of the increased insulin resistance. If people lose weight, become more active and lower the cellular demand for insulin, there is a decrease in blood-insulin levels, and cells again become sensitive to insulin. Later in the course, failure of the beta cells of the pancreas with absolute insulin deficiency may develop."

Previous studies at the University of Vermont have shown that when

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volunteer subjects overeat and gain weight, they develop insulin resistance which is reversible. Recent studies at the Vermont General Clinical Research Center by Drs. Stephen Phinney, Edward S. Horton, John Hanson and Sims were designed to measure how well patients following severely restricted diets could engage in endurance exercise. Six young obese adults, ranging in weight from 164 to 216 pounds (obese in relation to their individual height), were chosen for an eight-week study in the Vermont GCRC, supported by the DRR and the National Institute of Arthritis, Metabolism, and Digestive Diseases. They were given a daily diet of 1.2 grams of lean meat per kilogram of ideal body weight. The diet was supplemented with minerals and vitamins. The subjects also underwent closely monitored moderate exercise, measured on a treadmill.

In the study they found that during moderate exercise following six weeks of dieting, muscle glycogen was not used even though there was adequate reserve. They felt well and alert. Their capacity for moderate exercise on the treadmill had increased by more than 50 percent. During the six-week period of dieting, the subjects lost an average of 23 pounds, two-thirds of which was fat.

"We regard such severely restricted diets only as an adjunct treatment in the severely overweight," says Dr. Sims, "and for some of those who have diabetes, hypertension, or other medical problems which may be relieved as they lose weight. We do not feel that supplemented fasts are necessarily hazardous, but there are certain contraindications. Protein-supplemented diets have been used inappropriately for some people with mild obesity." The protein-supplemented diet with vitamin and mineral supplements used in this trial is nutritionally complete, but because of the absence of carbohydrates, the body had to switch metabolic mechanisms.

During prolonged exercise, people burn fatty acids and ketone bodies. The metabolic state of ketosis is a reflection of an inadequate supply of

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carbohydrate. Insulin levels drop and other hormones, such as glucagon and cortisol, increase. Fat is mobilized. Controlled studies are in progress with varied diets and types of exercise to determine whether marked restriction of carbohydrates is indeed critical or desirable for suppression of appetite, conserving body protein and enabling exercise to be combined with accelerated weight loss. Until such evidence is available, Dr. Sims admonishes that the patient undergoing rapid or large weight loss should not be encouraged to indulge in strenuous exercise.

Prehistoric man, Dr. Sims points out, lived in a state of starvation with intermittent feeding, which is uncommon for most people today. "Americans rarely miss a meal."

"Overeating alone does not cause diabetes," he maintains. "There are additional factors, probably inherited, that cause insulin resistance to progress into frank diabetes. The characteristic dual development of diabetes and obesity in adults is strongly inherited and is also associated with high birth weight in newborns." Oral agents are still used by an estimated 1.75 million Americans who have adult-onset diabetes. Even more overweight patients use insulin. Dr. Sims believes that at least in the early stages of their disorder, most of these overweight diabetics are treated inappropriately because they are not ketotic and not dependent on exogenous insulin.

"When you treat patients with insulin," he says, "they frequently begin a cycle of increased weight, increased insulin resistance, and higher blood-sugar levels -- all of which may lead to cardiovascular problems. During infection or acute illness or late in the course of their disease, if true insulin deficiency develops, insulin will be needed. Many, and probably most, of these people are spending large amounts of money for medication that is counter-productive to their health. We are wasting our resources if we treat

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with a predominantly pharmacologic and symptomatic approach."

The Vermont team is working on how to help the patient to maintain weight loss. They suspect that the combination of increased physical activity combined with dietary restriction may be more effective, since physical training even without weight loss improves insulin sensitivity.

For further information on this study, write to Dr. E. A. H. Sims, Professor of Medicine, Department of Medicine, University of Vermont College of Medicine, Givin Building, Burlington, Vermont 05405.

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News & Features FROM NIH

NARCOTIC ANTAGONIST INCREASES PAIN IN UNANESTHETISIZED PATIENT

Naloxone is a drug that reverses the pain-relieving effect of narcotics such as morphine. Studies of pain control at the NIH's National Institute of Dental Research in Bethesda, show that when naloxone is used alone it may increase surgical pain in comparison to no treatment. On the other hand, an inactive substance (placebo) reduces surgical pain when compared to no treatment.

Richard H. Gracely, Ph.D., and Ronald Dubner, D. D.S., Ph.D., collaborated with a team of NIDR dentists in their research on surgical pain. They explain that their findings are a first step toward showing that pain relief from placebos may be brought about by endorphins, the brain's own natural pain-relieving substances. Further research is needed to show whether endorphins are released during surgery or following administration of a placebo.

Answers to some difficult questions about pain are emerging from recent studies showing that the body can minimize pain by an innate mechanism. The brain itself releases molecules called endorphins (endogenous morphine-like substances). These molecules block the transmission of pain impulses by the sensory nerves with the result that pain sensations are blocked. Narcotics (such as morphine) block the same neural pathways, but their effects and those of the endorphins can be negated by naloxone. Hence, naloxone is used in pain research to distinguish morphine-like mechanisms of pain relief from other mechanisms.

In the past, lack of objective methods for measuring various aspects of pain has greatly hindered research. The NIH group has separated pain sensations from the emotional components of pain by means of descriptive word scales. These

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"descriptor differential scales" have been validated and are now being compared with "visual analog scales" for the ability to discriminate among various intensities and aspects of pain.

The visual analog scale is a straight line (usually 10 cm long) labeled at one end "no pain" and at the other "worst pain ever." Along this line patients mark the place that indicates the degree of pain. The descriptor scales contain one of 12 words describing either the unpleasantness or the intensity of pain in the center of a line. Patients mark one of ten spaces on either side of that word that best fits their perception of how much more or less pain they feel than the word suggests. The scientists find that descriptor scales are more sensitive than analog scales, especially for the unpleasantness of pain.

The subjects were 64 adults who required extractions of lower wisdom teeth. The dentists used a short-acting local anesthetic (2 percent lidocaine without epinephrine). No sedatives were given. Under these conditions most patients feel discomfort within an hour after extraction. All the extraction patients were asked to rate the intensity and unpleasantness of their pain by visual analog scales at 60, 110, 130, and 180 minutes after receiving the anesthetic. Some patients also rated pain with descriptor scales at 65 and 165 minutes. Two hours after the anesthetic, 18 received an injection of naloxone in solution, 24 received the placebo, an injection of the solution without naloxone, while 22 were not treated. Neither patients nor those giving the injection knew what substance was being administered.

After the local anesthetic wore off, pain increased steadily in the untreated patients. It also increased in placebo group but more slowly after the injection. In the naloxone group, for about 20 minutes after its injection pain decreased; thereafter it sharply increased.

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The scientists attribute this contradictory response to naloxone to a probable increase over time in the amount of the drug that acts on cell receptors in the brain. They note that low doses of naloxone have been reported to reduce pain, whereas high doses are said to increase pain.

These findings were reported in a paper titled "The effect of naloxone on multidimensional scales of postsurgical pain in nonsedated patients" by Gracely, R.H., Deeter, W.R., Wolskee, P.J., Wear, B.L., Sayer, J.S., Heft, M.W., Sweet, J., Butler, D., and Dubner, R. The paper was presented at the Society of Neuroscience annual meeting on November 4, 1979 in Atlanta.

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News&Features
FROM NIH

"PETT" SCAN DISPLAYS HUMAN BRAIN IN ACTION

NIH's National Institute of Neurological and Communicative Disorders and Stroke has awarded $5.7 million to expand research on a new technique using a radioisotope and a scanning device that allows neuroscientists to watch the human brain in action.

The technique is called positron emission transverse tomography (PETT).

A patient being studied by PETT is injected with or inhales a biochemical such as glucose, ammonia, or oxygen that has been tagged with a short-lived radioisotope. The radioactive tag emits positrons--charged particles detectable by a computerized imaging device. A scanning detector then follows the tagged compound's progress through brain tissue. Chemical activity is displayed on a T.V. screen as a grid of color patterns, much like a patchwork quilt.

"PETT will allow researchers to observe patterns of chemical activity that take place in the brain during speaking, hearing and thinking; to evaluate changes in brain chemistry before, during and after a stroke; and to determine the response of a brain tumor to drug treatment," said Dr. Donald B. Tower, Institute Director. "With PETT we will also be able to see the process of formation of brain lesions in multiple sclerosis and probe for biochemical abnormalities in disorders such as Huntington's disease or Alzheimer's disease."

Dr. Tower said that PETT is not a diagnostic technique at this early stage of development. It is too expensive and complicated. "But it is going to allow us to do extraordinary things in research, things we have never been able to do before," he said.

The technique is significantly different from the computerized axial

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tomograph (CAT) scanners now well known in diagnostic medicine. The CAT scan takes a still picture of the structure of an organ, allowing physicians to see abnormalities. PETT displays chemical activity within the brain as the activity occurs.

"What CAT scans have done for our ability to visualize the anatomy and structural pathology of the intact brain, PETT promises to do with respect to brain metabolism and function," said Dr. Tower.

The institutions and principal investigators who received the awards are:

-- Dr. Martin Reivich
University of Pennsylvania
Philadelphia, Pennsylvania

-- Dr. Henry Wagner, Jr.
The Johns Hopkins University
Baltimore, Maryland

-- Dr. Alfred Wolf
Brookhaven National Laboratories
Upton, New York

-- Dr. Alan Lockwood
University of Miami School of Medicine
Miami, Florida

-- Dr. David Kuhl
University of California, Los Angeles,
Los Angeles, California

-- Dr. Jerome Posner
Sloan-Kettering Institute of Cancer Research
New York, New York

Earlier studies supported by grants from the Neurology Institute are already under way at Washington University in St. Louis, Missouri, and at Massachusetts General Hospital in Boston, Massachusetts.

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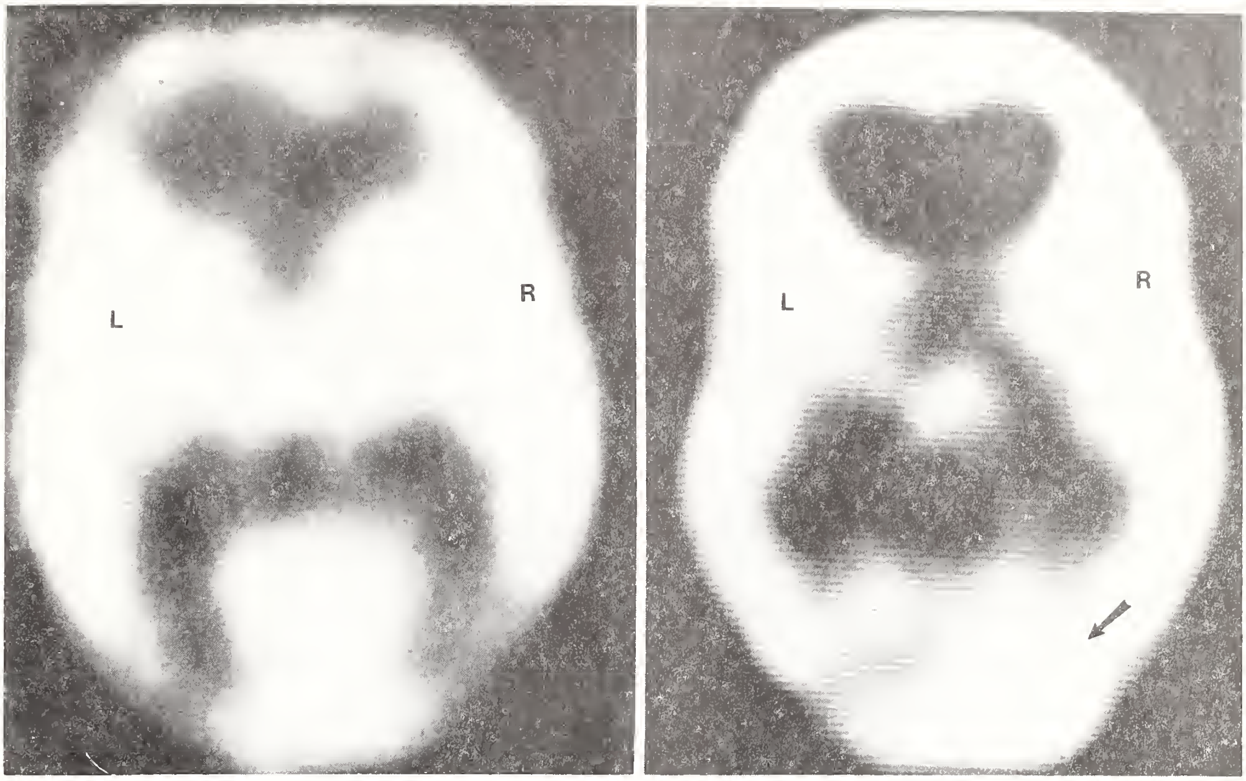

In contrast to the CAT scanner which uses X-rays to produce a still picture, the PETT scanning device utilizes gamma rays to produce a dynamic, functional picture. The cross-sectional view of a human brain above shows the effect of increased glucose metabolism in the visual center (see arrow) after stimulation by light in the left visual field. (NIH Photo #1632)

# # #

News&Features FROM NIH

IODINE INTAKE LINKED TO HYPOTHYROIDISM IN BABIES

By Joyce F. McCarthy

Pregnant women should watch their iodine intake. Hypothyroidism, or deficient thyroid gland function, is characterized by a slow metabolism and delayed development. This condition can be transiently induced in the fetus and perhaps the newborn by the exposure of the mother to pharmacological doses (excess amounts) of iodine. The hypothyroidism is usually temporary and completely disappears after exposure stops.

Iodine has been shown to easily cross the placenta of mothers given medications or substances containing large quantities of iodine. For example, in those women who received an iodine-containing dye for use in fetal X-rays, six of seven newborns had temporary hypothyroidism. This suggests that the normal fetal thyroid is very sensitive to the adverse effects of iodine on thyroid function.

Betadine, an iodine-containing antiseptic used in hospitals, has been found to induce temporary hypothyroidism in premature infants bathed in the solution. Hypothyroidism may also be induced in adults with underlying thyroid disease who are exposed to the chronic administration of pharmacologic doses of iodine.

Researchers at the University of Massachusetts Medical School, supported in part by a grant from NIH's National Institute of Arthritis, Metabolism, and Digestive Diseases, studied iodide. Daily doses of 1 to 2 mg. of iodide were administered to pregnant and nursing Sprague-Dawley rats and the iodide effects on fetal and newborn thyroid function were evaluated. The researchers found that iodide administered to the pregnant and nursing mothers induces hypothyroidism in the newborn and neonatal rat which disappears by approximately ten

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days of life. Evidence for hypothyroidism was obtained by an increase of the serum TSH concentration and a decrease in the serum T_4 and T_3 concentrations. Thyroid function returned to normal from 18-60 days in spite of continued iodide administration to the weanling and immature rats. There was no effect of iodide administration on thyroid function in the mothers.

The first two weeks of extrauterine life in the rat resembles the latter half of human pregnancy. These results suggest that the chronic administration of pharmacologic doses of iodide should be avoided during pregnancy in view of the possible adverse effects of the transplacental passage of the iodide on fetal thyroid function.

It may be suggested that iodide-containing medications given to women during pregnancy and nursing may induce transient hypothyroidism in the fetus and newborn. Also, it is a fact that the mammary gland actively concentrates and secretes iodide into the milk.

The present findings in the perinatal rat and the occurrence of human fetal hypothyroidism following excess quantities of iodide exposure during pregnancy strongly indicate that iodide should not be given to human pregnant and nursing mothers. The significance of early recognition of hypothyroidism during the newborn period is very important. Diagnosis and treatment at the earliest possible time in infancy is of greatest importance in avoiding permanent intellectual and developmental impairment.

Since the effects of iodide during perinatal life cannot readily be studied in humans, this perinatal rat model can be exploited to further study the adverse effects of excess iodide during perinatal life. The study of the mechanisms by which iodides induce hypothyroidism during perinatal life have been greatly facilitated and may lead us closer to solving the problems of

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iodide-induced thyroid disease.

This research was conducted by Drs. Lewis E. Braverman, Theodor Theodoropoulos, and Apostolos G. Vagenakis from the Division of Endocrinology and Metabolism, University of Massachusetts Medical School, Worcester, Massachusetts. This article appeared in a recent issue of *Science*, Vol. 205, No. 4405.

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News&Features FROM NIH

NEW CHEMICAL ANALYSIS USED TO DETECT ENVIRONMENTAL TOXINS

NIH chemists are developing a new way to evaluate the toxicity of environmental contaminants by determining the relationship between toxicity and the size, shape, and symmetry of chemical molecules.

"This new approach to chemical screening for toxicity may provide data useful in selecting for further testing chemicals that are most likely related to the cause of cancer, thus saving crucial time and money," Dr. James McKinney of NIH's National Institute of Environmental Health Sciences recently reported to the Chemical Congress in Honolulu, Hawaii.

Dr. McKinney is Chief of the Institute's Laboratory of Environmental Chemistry, which has pioneered development of this approach.

Traditionally, toxicity studies have been based on laboratory experiments on microbes, tissue cultures, and whole animals. Though the chemical/molecular approach will not replace these older methods, it will give environmental scientists an important screening tool to select those chemicals most likely to show toxicity in more expensive animal and other tests, Dr. McKinney said.

Chemical analysis of molecular characteristics is being used on a variety of chemical environmental contaminants including PCB's, PBB's, chlorinated dioxins and furans, and related compounds such as naphthalenes, some of which have been associated with much publicized environmental contamination incidents.

Dr. McKinney explained that known physical characteristics of molecules are related to their degree of toxicity. This, he added, has been determined through animal experiments using the guinea pig, which is especially sensitive to the chemicals being tested.

The chemists' role in environmental health sciences has only recently been

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fully realized," Dr. McKinney said.

The National Institute of Environmental Health Sciences in Research Triangle Park, N.C., is the principal federal agency for biomedical research on the effects of environmental agents on health, and the only one of the National Institutes of Health not located in Bethesda, Md. NIEHS recently elevated its Chemistry Section to Laboratory status in recognition of chemistry's emerging role in environmental health sciences.

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News & Features FROM NIH

MAJOR CHILDHOOD TOOTH DECAY STUDY LAUNCHED BY NIDR

A major field study to determine the prevalence of dental disease among American children and the treatments needed, was recently announced by NIH's National Institute of Dental Research. Tooth decay is the most common childhood disease.

More than 40,000 students, in classes ranging from kindergarten through high school, will participate in the study.

The study is to be completed by June 1980.

Dr. David B. Scott, Director of the National Institute of Dental Research said, "There have been previous studies of the extent of tooth decay, but this one will include a much larger sample of school children drawn from the full range of income levels and representative of both rural and urban groups.

"Now that methods to prevent tooth decay are being widely used, we must have a reliable reference against which to measure public health effects, as well as to identify segments of the population that need special help."

WESTAT Inc. of Rockville, Maryland, will conduct the survey under contract with the Institute in at least 1,820 classrooms in public, private, and parochial schools in seven geographic regions of the continental United States.

The survey team of eight dentists attended a 3-day training course conducted by the Institute in July and started visiting schools in September to conduct the dental examinations.

All the children will have identical examinations:

(1) A check for tooth decay or fillings on the surface of every primary and permanent tooth, or for missing teeth.

(2) An examination to record the degree and location of gum inflammation

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and the need for instruction in personal oral hygiene or professional tooth cleaning.

(3) Following categories established by the World Health Organization, a determination of the treatments needed to correct or restore each child's dental health.

(4) A notation of previous or current orthodontic treatment.

On forms granting permission for each child's participation, parents will be asked to supply information on age, sex, race, and family income.

The Institute, using the present study as a baseline, plans to repeat the survey at intervals to detect changes in the incidence of tooth decay in any region, to target special emphasis programs toward high-risk age groups, and to measure how effectively new preventive measures have reduced dental decay.

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News & Features FROM NIH

L-DOPA REJUVENATES MOVEMENT CONTROL IN AGED RATS

Research on rats suggests that age-related changes in the central nervous system may be responsible for many of the disturbances in movement that are seen with advanced age and that this impairment can be reversed by drug therapy.

With research support from NIH's National Institute on Aging, Dr. John F. Marshall, Department of Psychobiology, University of California, Irvine, has found that when compared with younger adult rats, aged animals move their limbs less vigorously during prolonged exercise. Such movement dysfunctions are strikingly similar to those seen in young adult animals that have sustained injury to dopamine-containing neurons in the brain.

Dr. Marshall's findings, reported in a recent issue of *Science* magazine, include evidence that the impaired function of the aged rats can be reversed by administration of L-dopa (the biosynthetic precursor of dopamine) or apomorphine (a dopamine receptor stimulant).

Research on aging has shown that elderly persons generally require more time to prepare for and carry out movements, pace themselves poorly in tasks requiring continuous performance, and fail to adjust their movements to compensate for their errors. At NIA's Gerontology Research Center, investigators have noted that ability to perform complicated tasks declines more quickly with age than the ability to perform simple tasks that don't call for coordination, such as pushing and pulling a stationary object. Historically, such changes have been thought to relate to decreased muscle strength or the accumulation of fat with age.

Similarly, numerous investigations in both animals and humans have indicated age-related changes in neurotransmission at brain dopaminergic synapses.

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It has long been known that the dopamine-containing neurons of the brain play a critical role in movement. Parkinson's disease, for example, is characterized by rhythmical muscular tremors, rigidity of movement, and similar disturbances which are clearly attributable to a loss of dopamine-containing neurons. Dr. Marshall's research provides the first clue that dopamine might play a role in the movement problems of healthy aged populations.

The dramatic rejuvenation of performance in aged rats holds great potential significance for understanding the movement disturbances of aging.

Reprints of Dr. Marshall's report are available from the National Institute on Aging, Information Office, NIH, Bldg. 31, Rm. 5C-36, 9000 Rockville Pike, Bethesda, Md. 20205.

###

News&Features
FROM NIH

PESTICIDE-EXPOSED VOLUNTEERS SOUGHT FOR TREATMENT STUDY

Individuals who know that they are suffering from pesticide poisoning are needed for a research study being conducted at the Medical College of Virginia, Richmond. Dr. Philip S. Guzelian, head of the research team, is investigating the possibility that the same techniques that helped eliminate Kepone from the bodies of infected chemical plant workers may also be used against DDT, dieldrin, aldrin, endrin, chlordane, polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs).

In order to test this hypothesis, Dr. Guzelian is making a national appeal for research volunteers. Individuals who know they are suffering from such pesticide poisoning and doctors treating such individuals are asked to notify him at the Medical College of Virginia so they might discuss the possibility of the affected patients becoming research volunteers.

The research volunteers will be hospitalized at the Medical College of Virginia General Clinical Research Center, a research unit funded by NIH's Division of Research Resources (DRR), and in part by the National Institute of Environmental Health Sciences. According to Dr. Guzelian, the Medical College of Virginia Clinical Research Center, one of 75 such units funded by DRR, provides a discrete study unit where ideally controlled conditions and specially trained personnel offer the best environment possible for quality health care and reliable research results.

In studies of chemical plant workers who had undergone Kepone poisoning while manufacturing the product, Dr. Guzelian noticed that the workers who absorbed the pesticide had developed manifestations of toxicity in several organs, including nervous system disorders, male liver problems, and decreased

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sperm production. In addition to these human manifestations, Kepone also has produced tumors in rodents.

During clinical trials, Dr. Guzelian's research team treated exposed workers with the drug cholestyramine, an agent often used to help lower cholesterol levels in the blood. The researchers found that cholestyramine helped increase the fecal elimination of Kepone sevenfold, meaning that Kepone stored in body tissue was eliminated much faster than normal. This effect in turn, decreases the possibility of the chemical becoming carcinogenic which could be a result of prolonged exposure. "We found that cholestyramine stimulated the elimination of Kepone by binding it in the intestine," Dr. Guzelian explains.

At that time, the clinical investigators thought that Kepone was reabsorbed from the intestine into the blood stream where it once again entered the liver and returned to the intestine in the form of bile. However, later studies showed that the source of Kepone in the intestine appears to be the gut itself, clarifying the binding affect of cholestyramine in the intestine. Dr. Guzelian and the research team found that eliminating Kepone from the exposed workers reversed the manifestations of poisoning evident when the workers were admitted to the study almost 3 years ago.

"As the Kepone was eliminated the acute toxic manifestations of Kepone poisoning involving the liver, nervous system, and testes largely disappeared." Dr. Guzelian and his associates would like to find out if cholestyramine can eliminate other pesticides from the body and reverse physical manifestations of pesticide poisoning.

Anyone interested in participating in such studies as research volunteers or physicians treating such potential research volunteers should contact

(more)

Dr. Philip S. Guzelian at the Medical College of Virginia, P.O. Box 267, MOV Station, Richmond, VA 23298.

Dr. Philip S. Guzelian and his colleagues from Richmond's Medical College of Virginia, are expanding their research efforts into the problem of pesticide poisoning. Their efforts are concentrated on finding ways of eliminating pesticides from infected individuals. The researchers are seeking affected people to serve as research volunteers. The patients will be hospitalized on the Medical College of Virginia General Clinical Research Center, a special research hospital unit funded by the Division of Research Resources, National Institutes of Health. (NIH Photo #1633)

# # #

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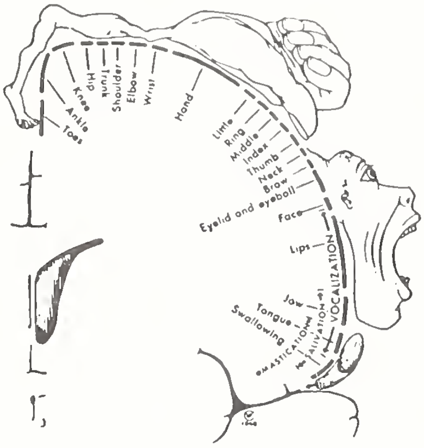

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News&Features
FROM NIH

MARIHUANA EXPOSURE REDUCES MOUSE COPULATORY AND SEX FUNCTION

By Joyce F. McCarthy

Male mice exposed to marihuana before birth have been found to have altered reproductive and copulatory behavior. The exposed mice were also found to have increased body weight and decreased testes weight.

Previous studies on female adult mice in late pregnancy found that cannabinoids (components of marihuana) cross the placental barrier and accumulate in a wide variety of fetal tissues. Cannabinoids can also pass from nursing mothers to the newborn through the milk.

It has been reported in earlier studies that the cannabinoids, tetrahydrocannabinol (THC), the main psychoactive component of marihuana and cannabinol (CBN), a nonpsychoactive component, affect reproductive functions and body weight regulation in male mice prior to sexual maturation.

In this study, the day before giving birth, the pregnant female mice received a 50 mg per kilogram of body weight oral dose of THC or CBN. Most mice weigh about 1½ ounces and they received approximately 1.5 to 2.0 mg of oral THC or CBN. This dose was chosen by the researchers after experimenting with amounts until the drug produced behavioral effects in the mice equivalent to those found in humans who are heavy marihuana users. One characteristic, the researchers watched for, was appearing glassy-eyed. It is known that this dosage will alter testis function in adult male mice.

The second dose of cannabinoids (THC or CBN) was given on the day of birth and treatment was continued daily for six days. Six males were culled from each litter born and then weaned at 21 days of age. They were then tested after reaching adulthood, between 60-80 days of age. Blood samples were drawn and tested for amounts of testosterone, luteinizing hormone (LH), and follicle-

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stimulating hormone (FSH), all necessary hormones for normal male sexual function.

The results show that adult male mice who had been exposed perinatally to THC had increased body weight and significantly decreased testes weight. Also, in both CBN and THC groups, copulatory behavior was significantly suppressed. However, those mice exposed to CBN during the perinatal period had reduced copulatory behavior and plasma FSH levels, suggesting that the two cannabinoids may have different effects on the function of the pituitary-gonadal axis. Mice are born much earlier developmentally than humans. Their time of birth corresponds to the latter half of human pregnancy. Therefore, these results may not apply to human pregnancy.

The mechanism of cannabinoid action on male sexual differentiation is not well understood. One hypothesis is that the THC and CBN interfere with testicular hormone production during critical periods of sexual differentiation and development. Cannabinoids may affect various brain regions, fertility, and sex-typical behavioral responses.

These findings suggest that exposure to cannabinoids during the perinatal period of sexual differentiation can result in permanent alteration in body weight regulation, pituitary-gonadal function, and copulatory activity in adult male mice.

It may be possible that these hormonal changes occuring during critical perinatal periods of sexual differentiation and development could result in long-lasting alterations in male reproductive function. And further, these changes may aid in the development of sexual confusion in the central nervous system which mediates copulatory behavior.

This research was conducted by Susan Dalterio, Ph.D., and Andrzej Bartke,

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Ph.D., of the Department of Obstetrics and Gynecology, University of Texas Health Sciences Center, and supported in part by NIH's National Institute of Child Health and Human Development. This article appeared in Vol. 205, p. 1420 of *Science* magazine.

###

PEPTIDE ANALOGUES MAY BE CONTRACEPTIVES OF THE FUTURE

Peptides, a particular group of amino acid configurations, may prove to be a new generation of contraceptives. The peptide analogues may be available for commercial use as early as 1983, according to National Institute of Child Health and Human Development-supported scientists at a press briefing held January 30 at NIH.

The peptide analogues (modified copies), are believed to have virtually no side effects, and could replace the widely used birth control pill for women and become the first successful chemical contraceptive for men.

The development of these peptide analogues opens an unexplored dimension in fertility regulation. Scientists believe that the analogues may serve as a practical postcoital contraceptive, make male contraception a reality, and suppress female ovulation on a regular basis with minimal side effects.

NICHD has started a major human clinical trials program to assess certain of these peptide analogues as fertility regulators in both males and females. The clinical trials are the direct result of basic research in brain hormones for which Andrew Schally and Roger Guillemin won the 1977 Nobel Prize in Medicine or Physiology. According to Dr. Gabriel Bialy, chief of the Contraceptive Development Branch, NICHD, the prize-winning scientists were able to develop an analogue of luteinizing hormone-releasing hormone (LHRH) and elucidate its chemical structure.

LHRH serves as a chemical messenger from the brain, said Dr. Wylie Vale, Salk Institute for Biological Studies. The hormone enters the bloodstream and is carried to the pituitary gland at the base of the brain. There, it stimulates the pituitary to secrete other hormones regulating ovarian function in

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women and the testis in men.

According to Dr. Vale, scientists have produced many LHRH analogues which either mimic or inhibit the action of natural LHRH. These substances have already proven successful in the diagnosis and treatment of women suffering from irregularities in their menstrual cycles. In addition, they have been used to induce ovulation in women who could not bear children because eggs were not released from their ovaries. The analogues have restored fertility in men who suffered from poor quality or insufficient sperm production.

Apparently, the dosage and timing of peptide administration is the significant factor affecting successful fertility regulation. Low doses administered to both men and women in an intermittent manner result in clinical improvement of infertility due to reproductive disorders. Higher doses reverse these improvements.

As successful fertility regulators for men, the peptides will suppress sperm formation while maintaining normal or near-normal levels of the male hormone, testosterone, reported Dr. David Rabin, Vanderbilt University. Men taking the drug should experience no loss of sexual desire or potency, he added.

The peptide analogues are thought to have several advantages over the synthetic steroids now in use as oral contraceptives. Synthetic steroids affect most cells in the body, are a burden on the liver, and resist rapid breakdown. LHRH analogues, however, have a more specific biologic action and are more rapidly degraded by the body.

###

POST-HEART ATTACK DEATHS NOT REDUCED BY ASPIRIN

The report of a major study sponsored by the NIH's National Heart, Lung, and Blood Institute (NHLBI) recommends that aspirin should not be routinely given patients who have suffered a heart attack.

The Aspirin Myocardial Infarction Study (AMIS) was designed to test the hypothesis, based on preliminary evidence, that regular administration of aspirin, can reduce mortality among heart attack patients. Dr. Robert I. Levy, NHLBI Director, said, "The difference in death rates was not statistically significant between the 2,257 patients who took the equivalent of three aspirins a day and the 2,267 patients who took a placebo. In fact," he added, "there were slightly more deaths due to recurring heart attacks in the group which took aspirin." Dr. Levy also noted that gastrointestinal side effects were considerably higher in the patients taking aspirin; symptoms suggestive of peptic ulcer, gastritis, or erosion of gastric mucosa occurred in 23.7 percent of the aspirin group as opposed to 14.9 percent in the placebo group.

"On the basis of these findings," Dr. Levy said, "the National, Heart, Lung, and Blood Institute would advise physicians not to give aspirin on a sustained basis to heart attack patients as a means of preventing another myocardial infarction."

The AMIS study involved 4,524 patients at 30 clinics, each of whom was followed for at least 3 years. It represents the largest completed study of aspirin in the post heart attack population. While clearly indicating that regular administration of aspirin does not reduce mortality for heart attack patients over a 3-year period, the AMIS study did provide some evidence

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supporting earlier findings that aspirin reduces the frequency of cerebrovascular events, such as stroke.

While mortality was slightly higher in the aspirin group, AMIS also found that the number of recurring non-fatal heart attacks was slightly lower in the aspirin group, but the difference was not statistically significant. AMIS did not attempt to validate the hypothesis that aspirin given immediately after a heart attack would be of value since the volunteer patients in AMIS did not enter the study until at least 2 months after having a myocardial infarction.

The National Heart, Lung and Blood Institute sponsored a workshop in late February at which scientists reviewed and analyzed studies dealing with aspirin and other drugs used to inhibit platelet aggregation. Some of these studies have suggested more promise for aspirin. Attendees at the meeting tried to reach a consensus as to which areas are not likely to provide definitive answers through additional research.

The AMIS study involved men and women from age 30 to 69. Each had a documented myocardial infarction (heart attack) from 2 to 60 months prior to their entry into the AMIS clinical trial. Each patient did not have any other major disease or known sensitivity to aspirin. The first patients were enrolled in early June, 1975. The last patient's follow-up visit was August 6, 1979.

###

ZINC-FORTIFIED CEREALS CAN PREVENT NUTRITION DEFICIT

By Karen Mayo

Zinc-fortified, ready-to-eat breakfast cereals were recently studied by scientists at the University of Colorado Medical Center, supported in part by NIH's National Institute of Arthritis, Metabolism, and Digestive Diseases. The study provided an opportunity to obtain biochemical data on the zinc nutritional status of healthy preschool and kindergarten children from middle-income families.

Zinc is a mineral which can be found in a wide variety of foods and is necessary for good human nutrition. It is a necessary constituent of a number of enzymes and therefore, an essential nutrient for man.

Recent studies have shown that zinc nutrition may be below normal and common in infants and children. The zinc content of many diets is considered to be, at best, only marginally adequate. This fact is attributable, in part, to losses of zinc during various types of food processing procedures and applies to some diets that are adequate in calories, protein, and other nutrients.

Previous studies in rats have indicated that zinc deficiency is manifested by retarded growth, loss of hair, and lesions in the skin, esophagus and cornea. Studies in young boys in Egypt and Iran indicate that a zinc deficiency results in retarded sexual development and reduced growth. In this study, 56 boys and 40 girls of preschool and kindergarten age from a private school in Denver participated. Most children came from middle-income families. All were healthy.

Baseline data pertaining to size, weight and body proportions were collected for each child. Dietary intake and frequency of food consumption data were taken. Blood samples, a 24-hour urine sample, and a small hair sample

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from the back of the head were taken. Occasionally, saliva from the parotid glands was also collected. In addition, taste perception was measured in those children who were older than 5 years of age, as zinc deficiency in man is accompanied by reduced taste perception.

After collection of baseline data, each family was supplied with ready-to-eat commercial-type cereals. The cereals were supplied to the entire family throughout the school year in quantities sufficient to meet their needs. Half of the children in the study received zinc-fortified cereals, and the other half (the control group) received cereals not fortified with zinc. The study was designed and implemented as a double-blind controlled investigation. No significant differences existed between test and control groups at the start of the experiment. The cereals which were zinc-fortified provided 25 percent of the daily United States Recommended Dietary Allowances per 1 ounce serving.

During the course of the school year, home visits were made to assess compliance with the study plan and to determine the quantities of cereals consumed. All baseline collections were repeated at the end of the school year, approximately 9 months from the start of the zinc fortification.

By the end of the period, the children (both girls and boys), who had received the zinc-fortified cereals, had significantly higher average zinc plasma levels than did control children. In addition, the girls in the zinc-supplemented group had significantly higher levels of zinc in their hair than controls at the end of the study.

There were no significant differences in other biological parameters including plasma copper and serum cholesterol. No significant differences in food intake or growth were associated with the consumption of zinc-fortified cereal.

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Zinc fortification of certain foods could be beneficial in helping to ensure optimal zinc nutrition and to prevent zinc deficiency. In 1974, the Food and Nutrition Board of the National Academy of Sciences recommended that nutrient fortification of cereal-grain products should include zinc, and the Commissioner of Food and Drugs published proposed fortification guidelines for breakfast cereal products that included zinc.

These findings were published in the December 1979 issue of the *American Journal of Clinical Nutrition*. The investigators included K. Michael Hambridge, M.D., Mary Noel Chavez, M.S., R.D., Ronald M. Brown, B.S., and Philip A. Walravens, M.D.

###

RAPID FREEZING CAPTURES TRANSIENT NERVE CELL STRUCTURES

The mysteries of a nerve cell's interior can now be examined. A new technique has been designed which freezes tissue so quickly--in one-thousandth of a second--that the brain's synaptic transmission can be examined avoiding any chemical interference.

The technique was developed primarily by Drs. John E. Heuser of the University of California at San Francisco, and Thomas S. Reese of NIH's National Institute of Neurological and Communicative Disorders and Stroke (NINCDS). The new technique was described at a recent NIH Science Writers Seminar.

The freezing device slams samples of tissue against a metal surface cooled by liquid helium. This "slam freezer," which is now built commercially, is capable of freezing living tissue in one to two milliseconds (msec).

A technique called "freeze fracture" is used to examine tissue once it has been frozen. This method has been used extensively at the NIH and elsewhere to examine the brain and spinal nerves. Freeze fracture reveals the interior of cell membranes, and has produced clear maps of receptors at synapses as well as important features of other neural membranes.

A limitation of the conventional freeze fracture technique is that this method cannot reveal how transmitter is released across the synaptic membrane. The chemical fixatives usually used to prepare tissues in freeze fracture are at least 100 times slower than the release process, which is completed 5-10 msec after a nerve impulse.

Exactly how transmitter is released was finally understood by Heuser and Reese when synaptic preparations were stimulated in the freeze slammer and

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frozen at the exact moment of transmitter release. This approach represents a significant improvement in preparing tissue for freeze fracture, and one which is also helping NINCDS scientists unravel the steps in the release of secretory material from gland cells.

The ultra-rapid slam freezing technique has important uses besides freeze fracturing, because ice crystal growth in the tissue is negligible and soluble components of the tissue are stopped in their living positions.

For example, Dr. Richard Ornberg of the NINCDS uses the freezing technique to prepare tissues for an electron microscope equipped with an X-ray spectrometer, an instrument that detects ions and elements in tissue inside an electron microscope. The distribution of calcium, which is known to be an important intracellular regulator of nerve and muscle function, can now be visualized. Other important intracellular components such as sugars or neurotransmitters can also be studied with this approach.

The slam freezing technique provides an important tool to aid the understanding of how disease agents act on synapses, as well as how synapses in the central nervous system function normally, after the administration of drugs, or in epilepsy.

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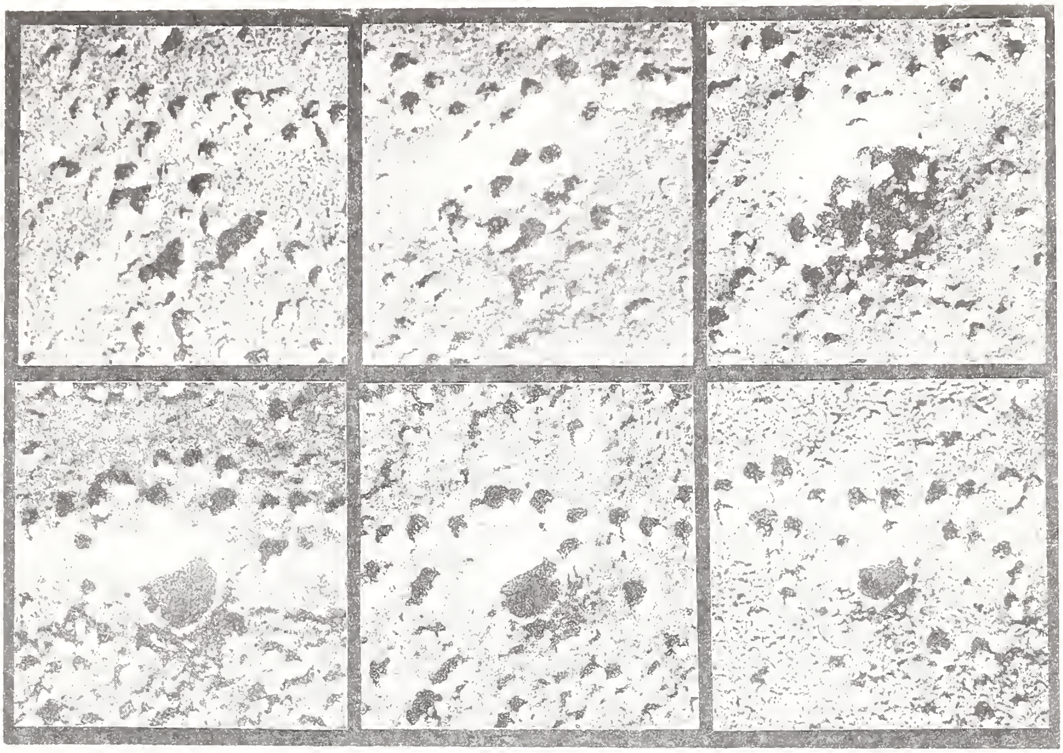

The release of neurotransmitter is shown in six free-fracture views (magnified 500,000 times) of progressive stages of synaptic vesicles opening and collapsing into the membrane of a synapse. The entire process takes place in less than 5 milliseconds, so it can seen only by rapid freezing of nerves. (NIH Photo #1634)

###

NEW INSIGHTS EXPLAIN MOVEMENT CONTROL BY THE BRAIN

Many recent insights into how we move are the result of studying brain cell discharges of monkeys performing learned movements. These studies have shown that some cells become active prior to voluntary movement, and some after. Consequently, a new understanding of the function and interaction of the different parts of the motor system has evolved.

The traditional view has been that the cortex (the outer region of the cerebrum) represented the highest level of motor integration, initiated all movement and controlled all aspects of movement. It now appears, however, that the situation is quite the reverse.

Dr. Edward V. Evarts, Chief, Laboratory of Neurophysiology, National Institute of Mental Health, reported at the NIH's January Science Writers Seminar, that the cerebellum and the basal ganglia may act in a more abstract and complex manner than the motor cortex. The motor cortex now is believed to be a final pathway through which basal ganglia and cerebellar systems transmit impulses initiating and guiding movement from the brain down to the spinal cord.

The spinal cord motoreurons which carry these directions are more directly connected to the motor cortex than to the basal ganglia or the cerebellum. (In addition, other connections descend parallel to the direct path from the motor cortex to the spinal cord. These connections are in other regions of brain stem nerve cells controlled by the cerebellum and motor cortex.)

The fibers running from the motor cortex to the spinal cord motoreurons are organized in such a way that each small motor cortical region (focus) controlling a particular movement, is surrounded by a "fringe" of motor cortex.

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This area has only partial control over the movement.

Neurons in the fringe for one movement are in the focus for another. Recovery from small cortical injuries may involve shifts of control from a damaged focus area to an intact fringe area, which eventually develops the ability to control the lost movement. If such shifts could be enhanced, it would be an important step in therapy for movement disorders.

Work on the basal ganglia has shown that they are particularly critical for controlling certain types of movement. Previous studies have shown that damaging the globus pallidus (a part of the basal ganglia) prevents a monkey from performing a previously learned arm movement if he cannot see his arm. The arm movement, however, can be performed quite easily when he is allowed to see what he is doing.

These experiments help to explain a clinical observation of patients with Parkinsonism: visually guided movements (such as playing tennis) may be relatively unaffected, even when other movements (such as walking and swallowing) are greatly impaired. This research shows that the basal ganglia are especially critical for internally generated movements (movements for which we do not rely upon feedback from the outside world). Therefore, basal ganglia damage apparently necessitates that motor control rely upon input from the outside world.

Work on the cerebellum suggests that one of its fundamental functions may be to help us learn and remember new movements, such as playing the piano. Further, it suggests that the ability of the motor system to adapt to learning special movements may be significant in cases where damage to other parts of the brain requires reorganization. Under these circumstances, the cerebellum may modify nerve function to compensate for impairment in damaged parts of the brain.

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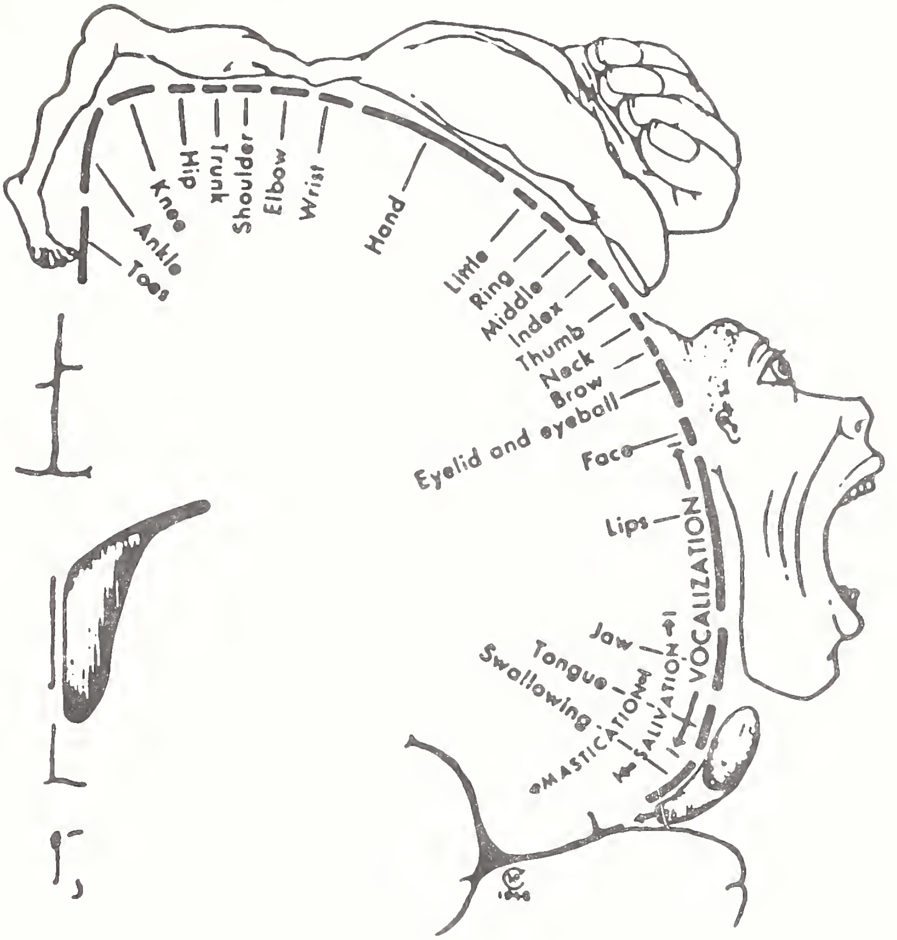

This illustration shows the various movements controlled by the motor cortex, the specialized cerebral subdivision in which the control of movement is engineered. Research on the motor cortex has shown that the laws of reflex action, long known to operate at the level of the spinal cord, also operate at the level of the cerebral cortex in the course of voluntary movements. Dr. Edward V. Evarts and his NIMH colleagues have gained many insights into how we move by studying the brain cell activity of monkeys as they perform learned movements. (NIH Photo #1635)

###

LABELLED GLUCOSE ANALOGUE MAPS BRAIN ACTIVITY

By measuring energy metabolism, it is possible to estimate the level of functional activity in the brain. Energy metabolism is closely related to functional activity in most tissues, including those of the central nervous system.

Dr. Louis Sokoloff, Chief, Laboratory of Cerebral Metabolism, National Institute of Mental Health, has developed a method which indicates those parts of the animal brain functioning at specific times. He described this method at NIH's January Science Writers Seminar. Using a radioactively labelled analogue of glucose, 14C-deoxyglucose ((14C) DG), measurements of glucose utilization can be taken simultaneously in all parts of the brain. It is now possible to map the level of functional activity in the central nervous system.

A change in the rate of glucose utilization (i.e., of glucose metabolism) by a local area of tissues suggests a change in the functional activity of those tissues. The recently developed procedure uses radioactive deoxyglucose ((14C) DG) to trace glucose metabolism in the brain. It is so designed that the concentration of radioactivity in a local area of tissue indicates the rates of glucose metabolism by that tissue.

The deoxyglucose (DG) method has become a useful tool for metabolic mapping of functional neural pathways, localizing active sites of centrally acting pharmacological agents, and for identifying regions of disturbed function in pathological conditions.

The concentrations of radioactivity in the local cerebral tissues are measured by a quantitative autoradiographic technique. The technique not only allows quantification of the actual rates of glucose utilization by the indi-

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vidual tissues, but the autoradiographs obtained provide pictorial representations of the relative rates of glucose utilization in all the cerebral structures. This can be seen in autoradiographs of 20μm serial sections of the entire brain. A functional, rather than merely an anatomical map of the entire central nervous system is now feasible.

The DG method was designed specifically to take advantage of the extraordinary spatial resolution made possible by quantitative autoradiography. The dependence on autoradiography designated the use of radioactive substrates for tracing energy metabolism, the labelled products of which could be assayed in the tissues by the autoradiographic technique.

The analogue of glucose, 2-deoxyglucose (DG), was chosen over glucose because its biochemical properties make it more reliable for tracing glucose metabolism. At the same time, glucose and its analogue are sufficiently similar biochemically. Both DG and glucose are transported between the blood and brain (across the blood-brain barrier) by the same carrier. Also, in cerebral tissues they both undergo the same chemical transformation when a phosphate group is added to them through the action of the enzyme hexokinase (phosphorylation by hexokinase). The resulting molecules are respectively either 2-deoxyglucose 6-phosphate (DG-6-P), or glucose 6-phosphate.

The biochemical advantage of using DG is that the product of its phosphorylation by hexokinase, DG-6-P, remains essentially trapped in the cerebral tissues during the experimental period. However, glucose 6-phosphate is further metabolized before the end of the experimental period.

The local rate of tissue glucose utilization is calculated from measured values found in the plasma of both glucose and its radioactively labelled analogue, (14C) DG, and in the tissues of 14C. By combining these values with computer-assisted image-processing techniques, autoradiographs can be trans-

(more)

formed into color illustrations. The actual rates of glucose utilization are encoded into specific colors and tints and distributed spatially in their actual locations within the nervous tissues.

The most dramatic demonstrations of the ability of the (14C) DG method to map functional activity in the central nervous system have been in the primary visual system of the monkey. In monkeys, as in all animals with binocular vision, particular areas in the brain (occular dominance columns) receive stimuli for a specific eye. The (14C) DG method has shown that if one eye is kept patched from the first day of life, its occular dominance columns in the visual cortex disappear by 3 months of age. The occular dominance columns that represent the functional eye broaden and appear to take over the adjacent areas of the cortex containing columns representing the patched eye.

In addition, the (14C) DG method has identified the specific points in the visual cortex that represent the blind spots of the eyes.

Recent developments in computerized emission tomography have provided the means to apply the DG method to man. Since emission tomography requires a different type of radiation, another radioactive form of DG has been synthesized and found to retain the necessary biochemical properties of DG. It is currently being used in human studies, and it is likely that this modification will prove immensely useful not only in clinical research but also in medical diagnosis.

###

PAIN TRANSMISSION TRACED THROUGH NERVOUS SYSTEM

Dr. Ronald Dubner of NIH's National Institute of Dental Research (NIDR) recently described studies indicating the superficial layers of the dorsal horns (areas of the spinal cord and medulla) as playing a major role in pain transmission. He explained his research findings, conducted in the Neurobiology Anesthesiology Branch, NIDR, at the January NIH Science Writers Seminar.

These superficial layers--the outer or marginal layer (MAR) and the next inner one, the substantia gelatinosa (SG)--receive exclusive input from small myelinated and unmyelinated nerve fibers. These fibers have receptor endings in the skin which respond to noxious (tissue-damaging) stimuli.

There are two categories of neurons in these layers that receive "pain" signals. One type, the nociceptive-specific neurons, respond only to stimuli causing tissue damage, such as heat or intense pressure, and are located mainly in the MAR layer. The other type, known as the wide-dynamic range (WDR) neurons, is activated by gentle mechanical stimuli, such as light touch and hair movement. However, these neurons respond maximally to noxious stimuli. WDR neurons are usually found in the deeper layers of the dorsal horns.

Dr. Dubner described NIDR research on the properties of these neurons. Both types of neurons transmit information to the thalamus, the integrating center for sensory input on its way to the cerebral cortex, and, both are located in the layers on either side of the SG (substantia gelatinosa). There are very few neurons, however, in the SG layer that transmit signals to the thalamus.

The neurons contained in the SG layer receive input from peripheral nerve fibers, descending axons from higher brain centers, and from neuronal

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dendrites located in the deeper layers of the dorsal horn. It appears that the SG layer modulates the output of the MAR neurons projecting directly to the thalamus.

One of these intrinsic neurons playing an important role in this modulation is being studied by NIDR investigators. This "stalked cell," as it is called, has its cell body located close to the MAR-SG border. Its dendrites extend into the deeper part of the SG and, occasionally, into the deeper layers of the dorsal horn. The cell's axon, however, arborizes extensively in the MAR layer among the dendrites of that layer's neurons which transmit information to the thalamus.

The stalked cells may therefore function as excitatory interneurons transmitting input from peripheral neurons receiving stimuli to neurons in the MAR layer that send signals to the thalamus. The stalked cell has also been reported to be strategically located for receiving descending modulatory information coming from supraspinal pathways projecting into the SG layer.

Dr. Dubner also discussed the variety of chemical neuromediators found in these layers of the dorsal horns, including enkephalin, GABA (gamma aminobutyric acid), serotonin, and norepinephrine. In addition, some evidence for the presence of opiate receptors and neurotensin in the SG layer has been found. These chemicals presumably play a role in the processing of sensory information but their functional role in pain transmission has yet to be established.

###

REVISED DNA GUIDELINES SIMPLIFY EXPERIMENT REQUIREMENTS

Revised guidelines for research involving recombinant DNA molecules were published by HEW in the January 29, 1980 issue of the *Federal Register*.

The guidelines lower the physical safety requirements for conducting most recombinant DNA experiments involving the bacterium E.coli K-12 to P1 + EK1 and eliminate the requirement for registration of these experiments with NIH. The experiments would not be exempt from the guidelines, however.

NIH is taking this action following a careful analysis of the precautionary steps necessary to assure the protection of the investigators doing this research and the general public. Scientists in the field generally believe that the use of this bacteria does not pose a significant hazard.

Recombinant DNA molecules result from recombination in the test tube of segments of deoxyribonucleic acid, the material which determines the hereditary characteristics of all living cells. The technology permits genetic information from very different organisms to be combined. Now about 6 years old, the research has already led to great increases in basic scientific knowledge and has demonstrated the possibility of producing, outside the human body, such important biological products as insulin, human growth hormone and, most recently, the virus-fighting substance known as interferon.

A decision document analyzing the public comments on the proposed revisions published in the *Federal Register* November 30, 1979, accompanies the guidelines. The comments overwhelmingly endorsed the revisions.

The steps announced today reflect changes in the guidelines recommended by the NIH Recombinant DNA Advisory Committee.

Copies of the material sent to the *Federal Register* (more than 150 pages)

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as well as copies of the letters received during the comment period (about 200 pages) are available from Dr. Bernard Talbot, Room 103, Building 1, NIH; telephone (301) 496-3561.

###

LARGEST BABOON BREEDING COLONY ESTABLISHED IN TEXAS

Originally imported from Kenya, South Africa, the yellow baboon (Papio cynocephalus) is the most popular Old World species used at Southwest Foundation. The animals have been found to be excellent for cardiovascular studies, pulmonary diseases, fetal and perinatal physiology, infectious viral diseases, and behaviorism. The domestic breeding program, supported by NIH's Division of Research Resources, will ultimately yield approximately 150 newborn baboons annually. (NIH Photo #1636)

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BABOONS (CONT'D)

The largest baboon animal breeding colony in the United States was put in operation about 4 months ago at the Southwest Foundation for Research and Education (SFRE) in San Antonio, Texas upon completion of a 6-acre semi-free-ranging corral.

Approximately 430 baboons were placed in the new corral, the most spacious primate outdoor enclosure in the country. The project will help ensure future supplies of baboon laboratory animals for biomedical researchers.

The funds for colony maintenance and part of the initial facility costs come from the Animal Resources Program of NIH's Division of Research Resources.

Twelve-sided in shape, the new corral will contain an observation tower with a food storage section below, a catch and holding area, a work area, a vehicle entrance, and feeding and watering devices in the holding area as well as around the perimeter of the wall. An irrigation system has also been installed to cover a portion of the area.

Long recognized for its research with baboons, the SFRE imports several hundred baboons annually from Kenya, East Africa. The Foundation, as well as the University of Texas Health Sciences Center at San Antonio, are currently heavily committed to projects using baboons as experimental animals.

The most popular Old World species used at SFRE is the yellow baboon *(Papio cynocephalus)*. The body size is probably one of the major advantages in using the baboon, averaging 30 kg. (66 lbs.) for males and 21 kg. (46.2 lbs.) for females. The baboon, which is easily maintained and reproduces well in captive colonies, has an average gestation period of 175 days.

Physiologically, the baboon is considered the right size for implant

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The new 12-sided baboon corral in San Antonio, Texas, contains over 430 baboons enjoying semi-free-ranging living conditions within the 6-acre area. NIH's Division of Research Resources supports the new breeding program in its efforts to ensure future supplies of baboon laboratory animals for biomedical researchers. (NIH Photo #1637)

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research, as well as for fetal investigations. The baboon fetus is approximately twice the size as that of the rhesus monkey. Newborns average about 750 grams (1.65 lbs.).

Major studies conducted with baboons at SFRE include cardiovascular disease with emphasis on atherosclerosis, hypertension, and hyperlipidemia; pulmonary diseases; fetal and perinatal physiology; infectious viral diseases; and behaviorism.

NIH researchers have been using SFRE baboons in the past and anticipate increased usage in the future. Among the NIH institutes involved are the National Cancer Institute, the National Institute of Allergy and Infectious Diseases, the National Institute of Child Health and Human Development, and the National Heart, Lung, and Blood Institute.

The starting ratio for the nucleus of the breeding colony will be 10 females to 1 male. It is anticipated that there will be approximately 150 newborn baboons annually.

The yearly harvesting of offspring will begin 2 years after the initiation of the project. The colony will serve as a national resource for the scientific community with concentrated use by NIH biomedical researchers in the field.

The breeding stocks, obtained from primate importers, have been carefully processed through a 5-week quarantine period during which comprehensive health evaluations were carried out.

A regular health care program has been established, including daily observation, treatment as required, annual physicals, and a disease monitoring program. The data will be computerized and will contain blood genetic and microbiological profiles as well as clinical chemistry of each animal.

"Each animal will be fully defined upon ultimate release to the biomedical researchers," says Dr. Gary Moore, principal investigator for the new SFRE baboon breeding colony.

" " "

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News & Features FROM NIH

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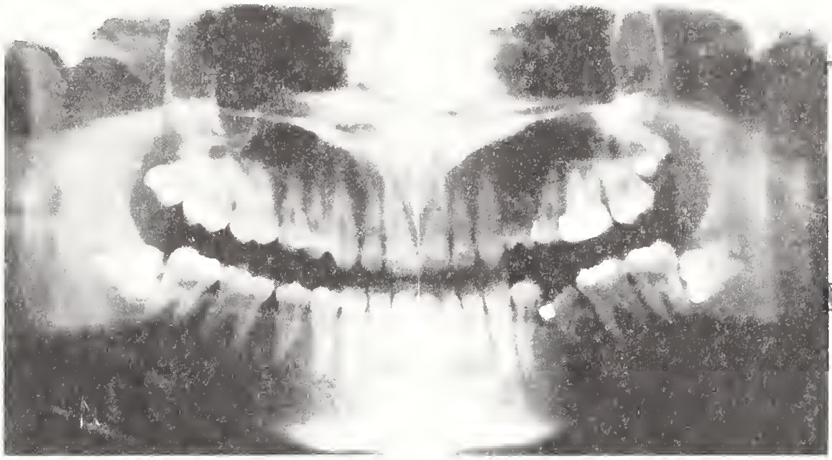

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News & Features FROM NIH

MALE IMPOTENCE MAY BE CAUSED BY HORMONAL DYSFUNCTION

By Joyce F. McCarthy

Impotence may be caused by a hormonal dysfunction rather than as a result of a psychological/emotional imbalance as has been alleged. Previously, 95 percent of all impotence has been diagnosed as psychogenic, but the results from this study indicate that any dysfunction at any location in the major hormonal system governing potency can lead to impotence.

Testosterone is the major gonadal steroid hormone responsible for maintaining normal potency. It is produced in the testes in the male and functions in the induction and maintenance of secondary sex characteristics. For hormonal dysfunction to be detected, it is very important for an impotent patient to be screened to determine the amount of his serum testosterone.

Dr. Richard F. Spark, Robert A. White, and Peter B. Connolly, M.S., from Beth Israel Hospital and Harvard Medical School, Boston, have found in research supported in part by NIH's Division of Research Resources, that of 105 consecutive impotent patients examined, 37 (35 percent) had unsuspected disorders of the hypothalamic-pituitary-gonadal axis. Once the specific defect was defined and appropriate therapy started, potency was restored in 33 of the 37 patients.

Research advances in the field of endocrinology and the results from this study indicate that it may be time to change our treatment approach to the impotent patient. Until the 20th century, the management and treatment of impotence was the exclusive domain of witch doctors and shamans. However, in 1912, Sigmund Freud tied the study of impotence with medical science and postulated that when a man unconsciously linked the sexual partner and his mother together the result was impotence. Unfortunately, treatment with psychotherapy has not proved to be consistently effective in alleviating impotence. Treatment failure rates reaching as high as 63-67 percent have

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been reported.

Various theories for the cause of impotence -- neurological, vascular, and hormonal -- have been investigated and recognized, but by the early 1970s, the theory that impotence was preponderantly psychogenic in origin was the general consensus. Since that time, refinements in technique and an improved understanding of endocrine physiology and pathophysiology have allowed for a more precise definition of "constitutional impotence", or abnormally low urinary testosterone levels.

Testosterone production by the Leydig cells (interstitial cells of the testes) is stimulated by secretion of LH (luteinizing hormone) from the pituitary gland. Pituitary LH secretion, in turn, is governed by the hypothalamic decapeptide LHRH (luteinizing hormone-releasing hormone). The entire hypothalamic-pituitary-gonadal axis exists as a classic endocrine negative feedback loop. Therefore, if there is a breakdown or major malfunction in the testes impairing their ability to secrete normal amounts of testosterone, testosterone levels fall and LH levels rise. The result is hypergonadotropic-hypogonadism.

When the potency defect is in the pituitary, LH secretion cannot be adequately augmented by stimulation with LHRH. As a result, normal LH stimulation to the testes cannot be maintained, and the result is hypogonadotropic-hypogonadism. If there is a primary defect at the level of the hypothalamus inhibiting LHRH secretion, this will consequently diminish LH release from the pituitary and can result in inadequate gonadotropin stimulation to the Leydig cells of the testes, resulting in low serum testosterone levels.

It is sometimes difficult to distinguish patients with hypothalamic disease from those with pituitary disease. But other researchers have found that patients with primary hypothalamic disease will increase LH secretion in response to long-term LHRH infusions, whereas those with primary pituitary disease will

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not.

In addition, there are two other conditions which can impair normal potency function which are not anatomic, and these are hyperprolactinemia and hyperthyroidism. Hyperprolactinemia is a condition in which potency cannot be restored even if serum testosterone levels are brought into normal range. It is believed that this condition may exert some degree of peripheral antagonism against the normal action of testosterone. However, intravenous injections of testosterone may be effective.

In hyperthyroidism, the defect in the hypothalamic-pituitary-gonadal axis seems to be located at the level of the testes and correction of the hyperthyroidism itself corrects this defect.

The temporal association of an unsettling life event and the development of impotence need not imply a cause-and-effect relationship between the two. The development of impotence is by itself sufficient cause for depression and would understandably stress otherwise stable interpersonal relationships.

The hormonal factors Dr. Spark and his colleagues investigated control a complicated chemical system that has only been elucidated during the last 10 years. This study was made possible by three major discoveries -- the demonstration in 1970 that the pituitary hormone prolactin (which stimulates milk secretion in the mammary glands) is found in both men and women, and the Nobel Prize-winning developments of a radioactive test for hormones and chemical signals produced by the hypothalamus, a gland at the brain's base which acts as a relay station for other glands.

In impotent patients, hormonal dysfunction is most frequently discovered only after screening serum testosterone levels have been obtained. If they are low, then further studies of pituitary function are warranted. Elevated serum testosterone levels suggest a possibility of hidden hyperthyroidism.

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Once the specific defect of the hypothalamic-pituitary-gonadal axis has been defined, appropriate therapy can be started, and in most cases potency can be restored.

This article appeared in the *Journal of the American Medical Association*, Vol. 243, No. 8, p. 750 (February 22/29, 1980).

###

WORKING WOMEN ARE NOT MORE SUSCEPTIBLE TO HEART DISEASE

The number of women working full time outside the home has multiplied in the last few years. By entering the 9-to-5 rat race, has their risk increased for coronary heart disease (CHD) over what it would have been had they remained housewives?

Generally no, according to a recent study by Drs. Suzanne Haynes and Manning Feinleib of NIH's National Heart, Lung and Blood Institute Epidemiology Branch. The 8-year study, using data from the Framingham Heart Study (which began in 1948), concluded that "working women did not have significantly higher incidence rates of CHD than housewives." However, some exceptions were found when women were placed in specific occupational and marital status categories.

Beginning in 1965, a 300-item psychosocial questionnaire was given to the 1,319 participants (352 housewives, 387 working women and 580 men) who were enrolled in the Framingham Study. The questionnaire assessed employment and occupational status, personality type, situational stress, reactions to anger, sociocultural mobility and family responsibilities. All of the participants were aged 45 to 64 and free from coronary heart disease at the start of the study. Occupations were classified into three categories: white collar, clerical and blue collar.

A working woman was defined as one who had worked outside the home for more than half her adult life. Regardless of employment status (currently employed, unemployed, retired) women reported more symptoms of emotional stress than men. In addition, working women experienced more job mobility than men, more daily stress and more marital dissatisfaction than housewives or men. All of these differences were statistically significant.

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Although the overall data indicate that working women did not experience statistically different incidence rates of CHD than housewives (7.8 vs. 5.4 percent), women in clerical occupations had nearly double the incidence of CHD (10.6 percent) that housewives had. CHD rates were also higher among working women who were or had ever been married, especially for those who had raised three or more children.

The study results indicate that women in clerical positions (secretaries stenographers, bank clerks, bookkeepers and sales personnel) are at higher risk of developing coronary heart disease than are other women. The risk increases with family responsibilities (i.e., having children), and is greater (21.3 percent) if a woman in a clerical occupation has children and married to a man doing blue-collar work. The most significant predictors of CHD among women in clerical occupations were suppressed hostility, having a nonsupportive boss and a lack of job mobility (staying in the same job for a long time).

Previously, it was thought that a man's lifespan was shorter than a woman's because of the man's occupation. Researchers were fearful that with more and more women entering the work force, the incidence of chronic diseases such as CHD in these women would begin to show the same mortality statistics as for men.

Dr. Haynes noted that "the Framingham data show that employment by women, in itself, is not related to an increased risk of coronary heart disease. In fact, the women who were employed the longest period of time -- the single, working women -- had the lowest rate of CHD." This article appeared in the *American Journal of Public Health,* February 1980, Vol. 70, No. 2, p. 133.

###

DES-EXPOSED WOMEN MAY HAVE INCREASED RISK DURING PREGNANCY

Women who were exposed to the drug DES before birth may face some increase of risk to pregnancies of their own, says a preliminary report from a continuing national study supported by NIH's National Cancer Institute.

DES is the synthetic hormone diethylstilbestrol, which, from the 1940s into the 1970s, was sometimes prescribed for women with possible pregnancy complications.

In *The New England Journal of Medicine*, March 13, 1980, investigators for the institute's project Diethylstilbestrol and Adenosis (DESAD) reported that the risk of an unfavorable pregnancy outcome among a group of women exposed before birth to DES was nearly one and three-quarters times that of a comparison group of similar women not so exposed.

Successful pregnancy outcome is the birth of a full-term (36-week) live baby. Unfavorable outcome is a miscarriage (spontaneous abortion before the 20th week), a premature live birth, a stillbirth or an ectopic pregnancy (outside the uterus and fatal to the fetus).

Dr. Ann B. Barnes, a Massachusetts General Hospital gynecologist and staff member of the Vincent Memorial Hospital, is the principal author of the report.

No difference in the ability to conceive a child was found between a group of 618 women exposed to DES before birth and a comparable group of 618 unexposed women.

On the question of childbirth, the number of study participants was adjusted to a total of 220 exposed women and 224 unexposed women to include only women who had gone through at least one pregnancy that did not end in an induced abortion.

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Among the DES-exposed women, 83 (38 percent) had unfavorable outcomes to their pregnancies, more than two-thirds of which were miscarriages. Unfavorable results occurred only among 50 (22 percent) of the 224 comparable unexposed women.

Most exposed women gave birth to at least one full-term live baby during the 5-year study. At least 81 percent of exposed women had had one or more favorable outcomes, compared to 95 percent of the comparable unexposed group. About half of those exposed women with unfavorable outcomes also had at least one full-term live baby.

"Until additional data have been collected by the project, any theory about what, if any, biologic mechanism might have caused the difference in pregnancy outcome would be speculation," Dr. Barnes concluded. "In this study for example, we could detect no difference in pregnancy outcomes between exposed women with visible structural changes of the cervix and vagina and exposed women who did not have such changes."

In addition, no relationships were found by the project scientists between pregnancy outcomes of the women exposed before birth to DES and 1) their mothers' prior medical histories of miscarriages or stillbirths, or 2) the medical history of the pregnancy that led to each daughter's birth.

Dr. Barnes emphasized that the participants in this study (both DES-exposed and the unexposed) had been selected through review of medical records in a variety of geographic locations. This method of selection ensures that the participants are most typical of the daughters of mothers who were given DES during their pregnancies and of comparable unexposed women in the general population.

Previous studies have shown such exposure to be linked with a slightly increased risk of a rare type of cancer of the vagina or cervix (the narrow

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lower portion of the uterus). It is also associated at times with the occurrence of noncancerous abnormal tissue and structural changes in the vagina or cervix.

"Clearly the story is just beginning to unfold," Dr. Barnes explained. "DES-exposed daughters may range in age from 8 years to the late thirties. Many of the women in the DES study project are just entering their reproductive years. Others may be following a national trend and delaying their first pregnancy. It may take many more years, perhaps the next decade, to obtain satisfactory answers to many of the relevant questions. In the meantime, for women exposed before their births to DES, careful monitoring of the course of their pregnancies is warranted."

Coauthors of the journal article with Dr. Barnes were Theodore Colton, Sc.D., consultant for the DESAD project from the Dartmouth-Hitchcock Medical Center, Hanover, N.H.; Dr. Jerome Gundersen of Gundersen Clinic, LaCrosse, Wis; Dr. Kenneth L. Noller, Peter C. O'Brien, Ph.D., Barbara C. Tilley, M.S., and Paul Hatab, M.S. of the Mayo Clinic, Rochester, Minn; Dr. Thomas Strama of Baylor College of Medicine, Houston, Texas; and Dr. Duane E. Townsend of the University of Southern California and Cedars of Lebanon Hospital, Los Angeles, Calif. The DESAD project, which started in 1975 comprises investigators at the above institutions.

###

NEONATAL RAT DES EXPOSURE AFFECTS SEXUAL DIFFERENTIATION

The exposure of newborn male laboratory rats (postnatal days 1-5) to two estrogenic environmental agents inhibits development of male characteristics as they mature. The effect is similar to castration at birth. This was the finding of a study by scientists at the National Institute of Environmental Health Sciences (NIEHS), in Research Triangle Park, N.C.

Estrogenic substances are at present widely dispersed as environmental agents, introduced into the biosystem through drugs, feed additives for meat animals, and environmental contaminants such as halogenated hydrocarbons.

The two estrogenic substances used in the research were diethylstilbestrol (DES) and estradiol-17B (E_2). Two other substances, testosterone propionate, an androgen hormone, and propylene glycol, a non-hormone, were given to separate groups of animals in the experiment to distinguish the action of the estrogenic substances. Both castrated and intact males, as well as intact females, were used in various dosing procedures for comparison.

Investigators Drs. Hugh A. Tilson and Coral A. Lamartiniere looked at six traits in groups of test animals. These were reproductive organ development, body weight, grip strength, exploratory behavior in a novel environment, and sperm development in testes of males.

In general, the intact males treated with estrogens were similar to castrated males and closer to female animals than intact males treated with non-estrogens. All males in the experiment were either castrated or given sham surgery, to eliminate any possible reaction to surgery as a variable.

The research is reported in a paper titled "Neonatal Exposure to Diethylstilbestrol Affects the Sexual Differentiation of Male Rats" appearing in

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Neurobehavioral Toxicology, Vol. 1, pp. 123-128.

Dr. Tilson is a pharmacologist in the Laboratory of Behavioral and Neurological Toxicology, and Dr. Lamartiniere is a research chemist in the Laboratory of Organ Function and Toxicology, both components of NIEHS. NIEHS is the principal Federal agency for biomedical research on the effects of environmental agents on human health, and the only one of the National Institutes of Health not located in Bethesda, Maryland.

###

NEWBORN HEARING IMPAIRMENT
LINKED TO VIRAL INFECTION

Clinical researchers from the Medical Center at the University of Alabama in Birmingham announced that they have developed an effective screening procedure to detect a viral infection common in newborns which they now believe to be the leading cause of hearing impairment in the United States. The announcement came in conjunction with an article in the February issue of *Pediatrics*, Vol. 65, No. 2, pp. 251-257.

Dr. Sergio Stagno, a pediatrician at the UAB Medical Center and lead author of the article, explained that the screening procedure detects cytomegalovirus (CMV), a common cause of intrauterine infection frequently transmitted to infants at or near the time of delivery. "Clinically, this congenital infection is largely asymptomatic in the newborn period," Dr. Stagno reported. "However, both overt disease and subclinical infections can lead, in a significant number of infected infants, to serious hearing problems which can appear at a later age. In fact, we now believe CMV is the leading cause of sensory neural hearing loss in children in the United States," Dr. Stango added.

Dr. Stagno said that both the development of the new screening procedure and the finding that CMV is the leading cause of sensory neural hearing loss in U.S. children are the direct result of research funded by the National Institute of Child Health and Human Development that took place on the Medical Center's General Clinical Research Center, a special 10-bed unit located in University of Alabama Hospitals. The unusual hospital unit is one of 75 such centers funded by the Division of Research Resources, National Institutes of Health. The centers are dedicated to the dual purposes of patient care and

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human research, with a staff specially trained and facilities specifically designed for those two roles.

Dr. Stagno explained that clinical research showed CMV infections also can result in growth retardation, learning disabilities, sight problems, and immune system disorders.

"For those with overt neonatal illness, manifestations may range from isolated organ system involvement to multiple organ system dysfunction with life-threatening potential," he said. "However, the most significant problem is an undetected hearing loss in the infected but asymptomatic newborn. It is critical that these infants be detected early so that management of the hearing loss and other manifestations can begin."

The UAB pediatrician said if the hearing loss is not detected early in life and intervention does not begin immediately the development of language is compromised and the learning process is slowed at a critical age. Therefore the development of a convenient, fast, accurate and low cost test to screen for CMV is a major medical advancement.

Dr. Stagno and his colleagues found the rheumatoid factor test to be an effective procedure to screen for CMV. The test involves taking a small amount of blood from a newborn and checking it for a unique type of antibody of significance in rheumatoid disease. The presence of the antibody in a newborn indicates the presence of an infection, most likely CMV. According to Dr. Stagno, the detection of the rheumatoid factor is as sensitive as tests used in the past to screen for CMV infections but, unlike the others, it produces no false positive results.

"The test results can be available in 2 hours, it is low cost, and it is convenient since it only requires a small amount of blood obtained from a heel-prick at birth," Dr. Stagno says. "We used the procedure in screening 1,412

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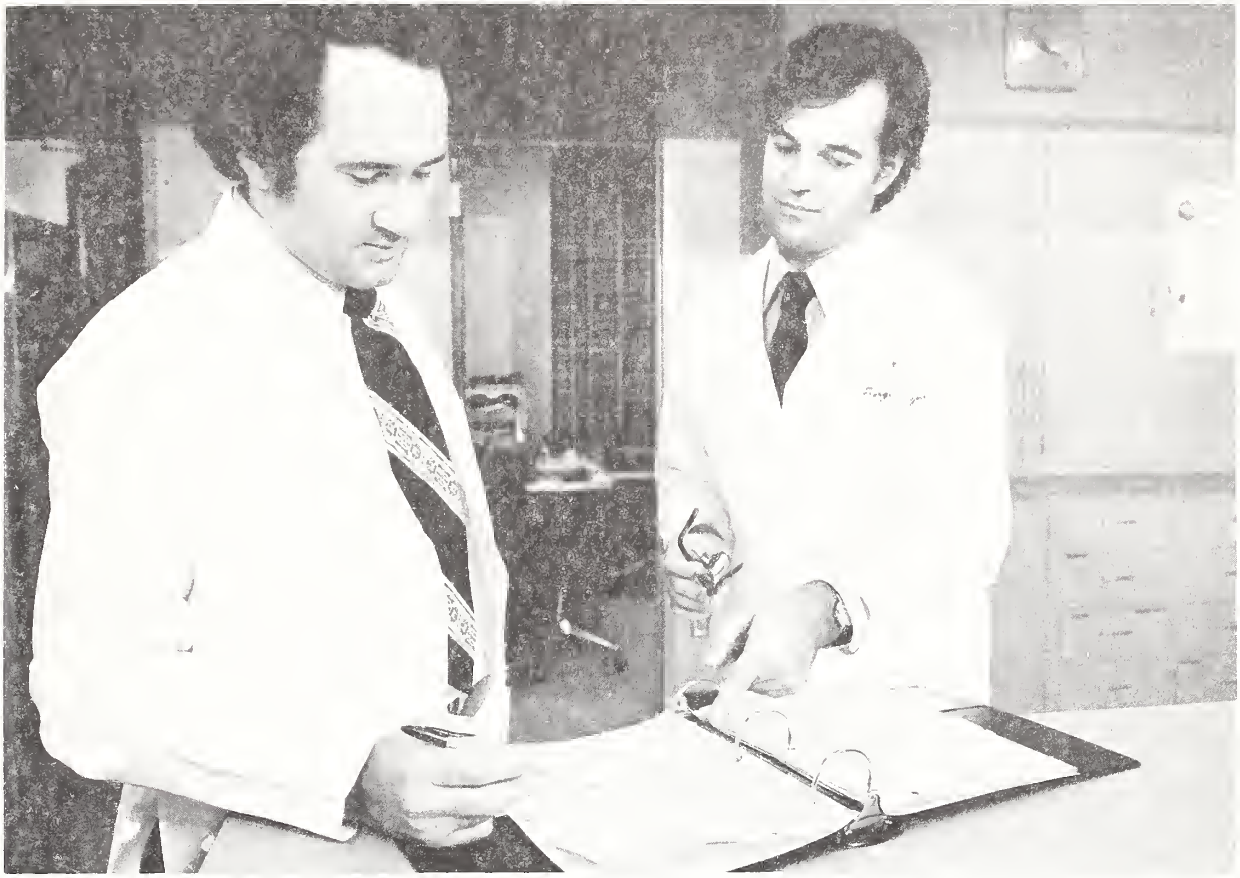

University of Alabama at Birmingham clinical researchers Drs. Robert Pass (left) and Sergio Stagno discuss the progress of patients with the common congenital infection cytomegalovirus. UAB investigators have developed a new screening test which can help detect cytomegalovirus in newborns. The test was developed as the result of investigation on the UAB General Clinical Research Center, a special research oriented hospital unit funded by NIH's Division of Research Resources. (NIH Photo #1638)

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newborns and found that the test was accurate in identifying 35 to 40 percent of infants with congenital CMV infection. While we would like that percentage to be higher, it appears from our study that the procedure identifies infected infants at the greatest risk for hearing loss and other medical problems."

UAB research has found that one to two percent of newborns have CMV infections, making it a significant health problem. "University Hospital in Birmingham and several other Birmingham hospitals now routinely screen for CMV," Dr. Stagno said.

"We feel that CMV is such a significant health problem that an even more accurate screening procedure must be developed that will gain acceptance and be used on a mass basis throughout the United States. With the use of the rheumatoid factor test we have made significant progress, but we are continuing our research to develop an even more accurate test that remains cost effective, fast and convenient."

As a result of the screening program used in Birmingham, Dr. Stagno and his colleagues now are closely following 300 children who have CMV infections. This represents the largest population of such patients in the world. These patients are followed through medical checkups at the University of Alabama General Clinical Research Center. The manifestations of the infection are managed at the University's Center for Developmental and Learning Disorders, a unique facility set up to deal with learning disabilities such as those seen in children with CMV infections.

"The Clinical Research Center has been the keystone to this entire effort," says Dr. Charles Alford, who pioneered UAB research into congenital infections some 15 years ago. "The Clinical Research Center allowed us to develop the current screening procedure for identifying newborns with CMV infections. It also has given us a research oriented patient care unit to follow these young-

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sters so we could learn as much as possible about the affects of congenital infections, such as CMV.

"It is research on the Clinical Research Center that taught us that CMV infections were the biggest cause of hearing loss. Follow-up research has taught us many other things about the long term effects of CMV infections. Much of the management of these patients takes place on the Clinical Research Center and the Center for Developmental and Learning Disorders.

"It also is likely that research supported by the Clinical Research Center will help us develop a better, more accurate screening test for CMV and will allow us to find a treatment for the disease."

Along these lines, preliminary work on developing an antiviral compound to treat CMV infections is already underway at the Center. For instance, one compound, called ara-A, has already undergone clinical trials with promising results on the treatment of neonatal herpes infection, and another compound, called ACV, has been approved for clinical trials that include herpes and CMV infected infants.

###

INFANT URINARY SCREENING DETECTS DEVELOPMENTAL DEFECTS

Urinary genetic screening tests are useful for detection of developmental abnormalities. Recently researchers from Yale University School of Medicine, reported in the *Journal of the American Medical Association* January 11, 1980, Vol. 243, No. 2. p. 126, that biochemical disturbances can be detected accurately by urinary genetic screening. This testing may be particularly useful for children diagnosed as autistic or exhibiting atypical childhood psychosis. They may be suffering from PKU (phenylketonuria) instead.

PKU is a physiological condition resulting from an excessive accumulation in the blood of an amino acid called phenylalanine and associated with mental deficiency. The infant affected lacks an enzyme which can break down phenylalanine in the blood. Phenylalanine then collects in the blood and phenylketones are present in the urine. A PKU test is done at birth to test for the presence of phenylalanine in the blood or phenylketones in the urine. To prevent the damaging effects of this enzyme deficiency, infants with PKU are fed low-phenylalanine diets which prevent accumulation of the substance in the blood.

PKU causes symptoms and signs that closely resemble childhood autism, a psychological state of mind characterized by daydreaming, hallucinations, and disregard of external reality. Usually autistic children are normal-looking but tend to exhibit highly bizarre behavior from an early age. These cases were often called childhood schizophrenics, but in recent years, studies have shown a portion are "autistic".

All children diagnosed as autistic display gross disturbances in communication (about half are mute); in relating to others, and in motor

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behavior (usually exhibited in hyperactivity, or in constant rocking movements). Previous studies in several countries have established an incidence of about 4.5 cases of autism per 10,000 births. It was formerly believed that autistic children suffered from an emotional rather than a neurological disorder. However, that opinion has been abandoned by most professionals as a result of a great amount of research suggesting a variety of neurological abnormalities in these children.

A total of 65 children were routinely studied by urinary amino acid screening methods in this 4-year study. Most of the research was conducted with the cooperation of the Yale University Children's General Clinical Research Center which is supported by NIH's Division of Research Resources. Fifty cases were diagnosed autistic and 15 as atypical childhood psychosis. Autistic subjects ranged in age from 3 to 19 years. Of the 65 subject urine samples tested by screening methods, three were found to have positive blood phenylalanine levels above 20 mg/dL. The three cases of PKU were further verified by repeated urinary testing and blood phenylalanine determinati The children were treated with low-phenylalanine diets and have shown improvement in functioning and developmental levels since treatment.

Many laboratories consider 4 mg/dL the upper limit of normal in assessing PKU. However, it has been recognized that not all infants who have classic PKU will have elevated blood phenylalanine concentrations within the first few days of life. This observation has led to much controversy in the design of neonatal screening programs. In some states, it has led to a revision of the upper limits of normal from 6 mg/dL to 4 mg/dL or even 2 mg/dL in some laboratories. In other states, the limits of normal values have been lowered, and in others, a recommendation to test a second time at age 2, 4, or 6 weeks has been suggested, For example, two missed cases of PKU in infants born in

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Connecticut within a 3-year period has led to a revision of the PKU screening program. Since the mandatory program began in 1966, 76 cases of classic PKU have been identified, and two known cases have been missed.

Urine tests are performed on newborn infants usually a day after their first feeding. U. S. Department of Health, Education, and Welfare regulations state that all newborn infants should be tested prior to hospital discharge and within the first 14 days of life, but no sooner than 24 hours after the first feeding. If infants are tested prior to age 4 days, a second test between 1 and 4 weeks of age is suggested. The Committee on Genetics of the American Academy of Pediatrics makes the same recommendations.

Findings from these studies and from previous studies indicate the value of the urinary screening test as a noninvasive, inexpensive test to correct inaccurate diagnosis of PKU-affected children. Early dietary treatment of the disorder preventing further progression of the disease will surely bring improvement. Urinary retesting may give new hope to parents with children suffering from autism and other atypical childhood behaviors.

This study was conducted by Drs. Thomas L. Lowe, Kay Tanaka, Margretta R. Seashore, J. Gerald Young, and Donald J. Cohen from the Department of Psychiatry; Department of Pediatrics; the Department of Human Genetics; and the Department of Psychology, Yale University School of Medicine, and the Child Study Center, New Haven, Connecticut.

###

EPILEPSY DRUG STUDIED FOR VARIOUS SIDE EFFECTS

The side effects of phenytoin (Dilantin), the drug commonly used to control epileptic seizures, was the subject of an international symposium held at the University of North Carolina at Chapel Hill. A review of the meeting, sponsored by NIH's National Institute of Dental Research, recently appeared in an issue of the *Journal of the American Dental Association.*

Attending the meeting were clinicians and researchers from both medical and dental disciplines who are prescribing the drug, studying its effects, or treating its side effects.

Since its development in the 1930's, phenytoin has been considered the drug of choice to control epileptic seizures--especially grand mal seizures. However, its undesirable side effects plague many of the over 2 million Americans who take the drug daily. These effects include overgrowth of the gingival (gum) tissues, abnormal blood conditions, and an increased risk of certain birth defects.

Overgrowth of gum tissue, sometimes almost burying the teeth in soft tissue, occurs most often and more severely in children than in adults under phenytoin therapy. Not only is the appearance unattractive, but dental hygiene becomes difficult and tooth decay and periodontal disease often result. Although dentists sometimes remove the excess tissue surgically, it often grows back.

The blood changes that follow phenytoin therapy in many individuals consist of lowered concentrations of immunoglobulins A,G, and M in the blood. The drug also frequently reduces the amount of immunoglobulin A (IgA) in saliva. The deficit in salivary IgA may be related to gingival overgrowth.

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A very important consequence of phenytoin therapy is that offspring of women taking the drug during the first 3 months of pregnancy have a six percent risk of serious birth defects as compared to the average risk of two percent (a threefold increase). Mental retardation is the most common defect. Overall growth is often reduced and so are head dimensions. Clefts of lip, palate, or both, and serious heart defects occur less frequently.

Some investigators reported animal studies that show phenytoin itself to be harmless. However, metabolism of the drug may cause by-products that are toxic. Other scientists, using radioactive phenytoin on inbred animals, presented evidence that one metabolic by-product, an epoxide, binds more to certain protein molecules in some strains than in other strains. In the bound state, the epoxide is thought to interfere with excretion and thus cause the concentration of the drug to rise to a damaging level in the fetus.

The findings from a number of studies indicate that a genetic predisposition is necessary for developing many of the reactions to phenytoin. In the epileptic patient, the reduction of immunoglobulins has a genetic association. In cell cultures, scientists find that cells (fibroblasts) of certain strains of animals multiply more actively under the influence of phenytoin than do similar cells from other strains of the same animal.

Experiments to separate the effects of epilepsy itself from the effects of therapeutic drugs are impossible to perform in humans but are being attempted in animals. One investigator found that a single dose, given on the 10th day of gestation and sufficient to bring the level of phenytoin in the sera of pregnant Ajax mice up to the levels in humans on this therapy, would increase the numbers of offspring with clefts 4-5 times more than the rate of spontaneous clefts in that strain.

Larger doses of phenytoin given on the same day caused clefts in almost

(more)

100 percent of the offspring. In this case the clefts were attributable to severely reduced growth of embryonic facial processes (lateral nasal process). This growth reduction correlates with the observations of others that there is a drug-induced loss of a meshwork of projections (cell processes) from embryonic mesenchymal cells. The meshwork appears to control the paths of cell migration in the developing head. A similar large dose of phenytoin given on the ninth gestational day resulted in limb deficits similar to the human short-finger defect.

Geneticists have shown that, in mice, certain genes control many drug-metabolizing activities. These same genes are also associated with birth defects, risk of cancer, and drug toxicity. Scientists now believe that a child's responses to phenytoin are not only affected by the nature of its mother's drug regimen and her genetic ability to metabolize the drug, but also by the child's own genetic constitution.

###

RADIATION EFFECTS DISCUSSED AT RECENT NIH MEETING

The future direction of federal research on radiation effects was the subject of a public meeting March 10-11, 1980, at the National Institutes of Health (NIH). The meeting, "A Proposed Federal Radiation Research Agenda", was sponsored by the Committee on Federal Research into the Biological Effects of Ionizing Radiation, which is chaired by Dr. Donald S. Fredrickson, NIH Director. Participating in the meeting were radiobiologists and other experts in the field, health officials, legal and ethical advisers, and representatives of consumer and public interest groups.

Ionizing radiation is electromagnetic (such as X-rays) and particulate (such as neutrons) radiations of sufficient energy to produce electrically charged ionizations in the atoms of a target (including living tissues). Radiation as a health hazard is of concern for several reasons, including increased use of radiation in medicine and industry, testing of atomic weapons, growing dependence on nuclear energy, and disturbance of terrestrial radioactivity through mining.

Current standards and guides in radiation protection are based on estimates of cancer and genetic risks, thus the degree of control advocated is directly related to the validity of the risk estimates. The goal of the federal committee is to develop a comprehensive, government-wide radiation effects research program which ultimately will reduce the uncertainty in radiation risk estimates.

The first day of the meeting was devoted to presentation and discussion of papers on the current status of radiation biological research and to issues of public concern. Among the issues are the legal, ethical, and economic constraints to developing an extensive knowledge base on the effects of radiation,

(more)

the environmental and hereditary conditions that may mediate those effects, and the applicability of animal and cellular radiation studies to humans.

On the second day, experts presented elements of research considered essential in a comprehensive federal effort. These elements include: epidemiology, genetics, therapeutic applications, and technology development. Public input was invited both during and after the conference.

Texts of the papers that were presented, as well as written public comments submitted in time for inclusion, have been printed and bound.

For further information concerning the meeting contact:

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###

CONSENSUS CONFERENCE DEFINES WISDOM TEETH REMOVAL CRITERIA

A consensus development conference on Removal of Third Molars was held recently by NIH's National Institute of Dental Research. The conference was held in an effort to reach general agreement on when and under what circumstances third molar extraction is advised and to identify areas where further research is needed.

The NIDR program brought together biomedical researchers, practicing dentists and physicians, and consumers, to review and evaluate the efficacy and safety of medical and dental technologies and procedures.

The conference participants divided into five workshops to explore the following issues: the effect of third molar removal on growth and development; the timing and technical considerations for third molar removal; prosthodontic and periodontic considerations for third molar removal; the morbidity of third molar removal; and the advantages and disadvantages of third molar removal. The workshop reports were presented and discussed by all participants on the final day and formed the basis for areas of consensus.

The workshop on advantages and disadvantages of third molar removal concluded that third molars, whether impacted or erupted, with evidence of follicular enlargement should be removed, and the associated soft tissue should be submitted for microscopic examination. Impacted teeth that develop soft tissue inflammatory conditions (pericoronitis) should also be removed because of their known potential for repetitive infection and morbidity. The workshop recognized, however, that the incidence and recurrence rate of pericoronitis

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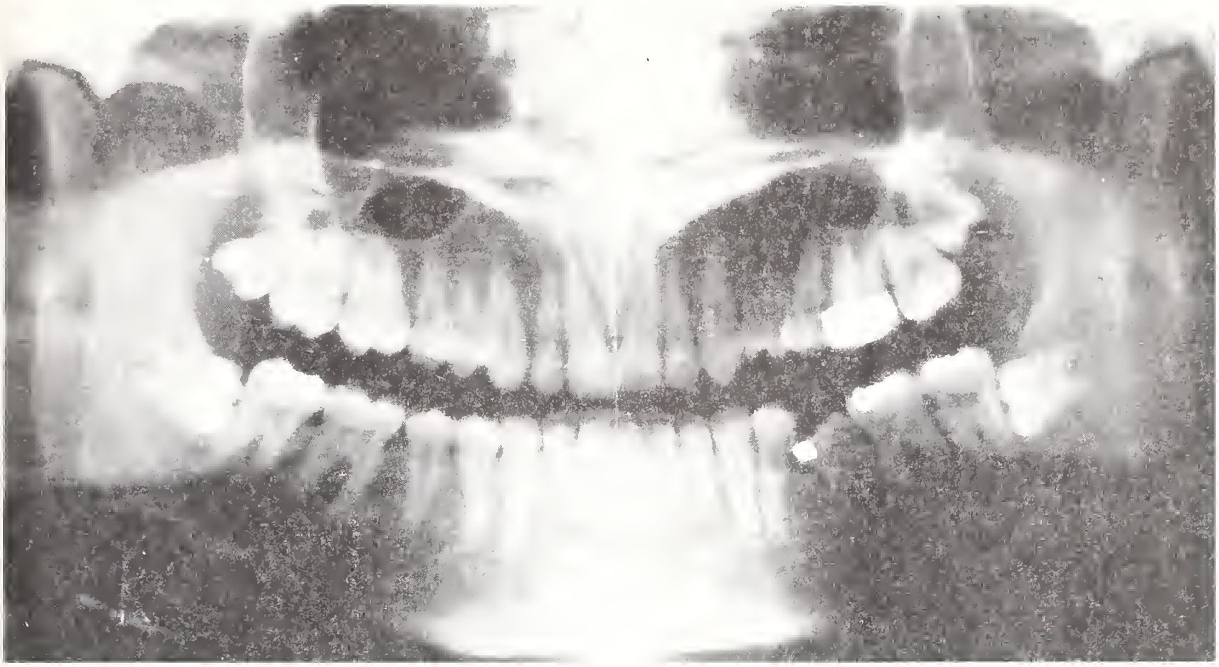
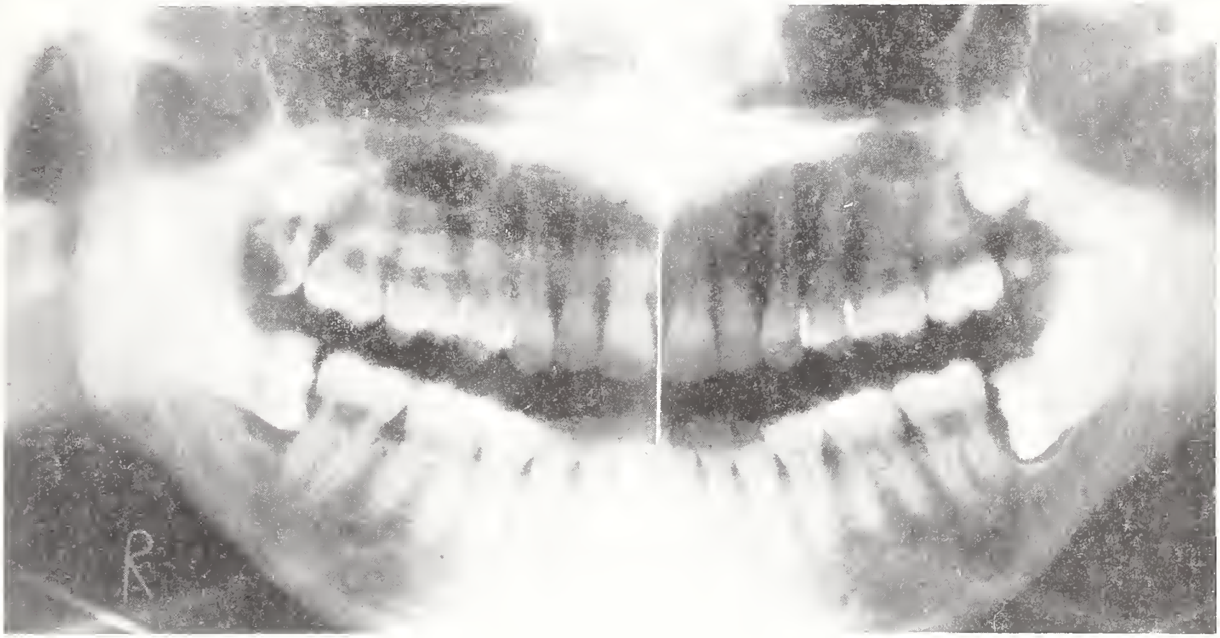


The picture above shows horizontally impacted lower third molars (left) and ankylosis-retained deciduous second molar (right). (NIH Photo #1639)



This picture shows horizontally impacted lower third molar with bone destruction adjacent to second molars; caries (upper right third molar); and impacted upper left third molar and supernumerary tooth. (NIH Photo #1640)

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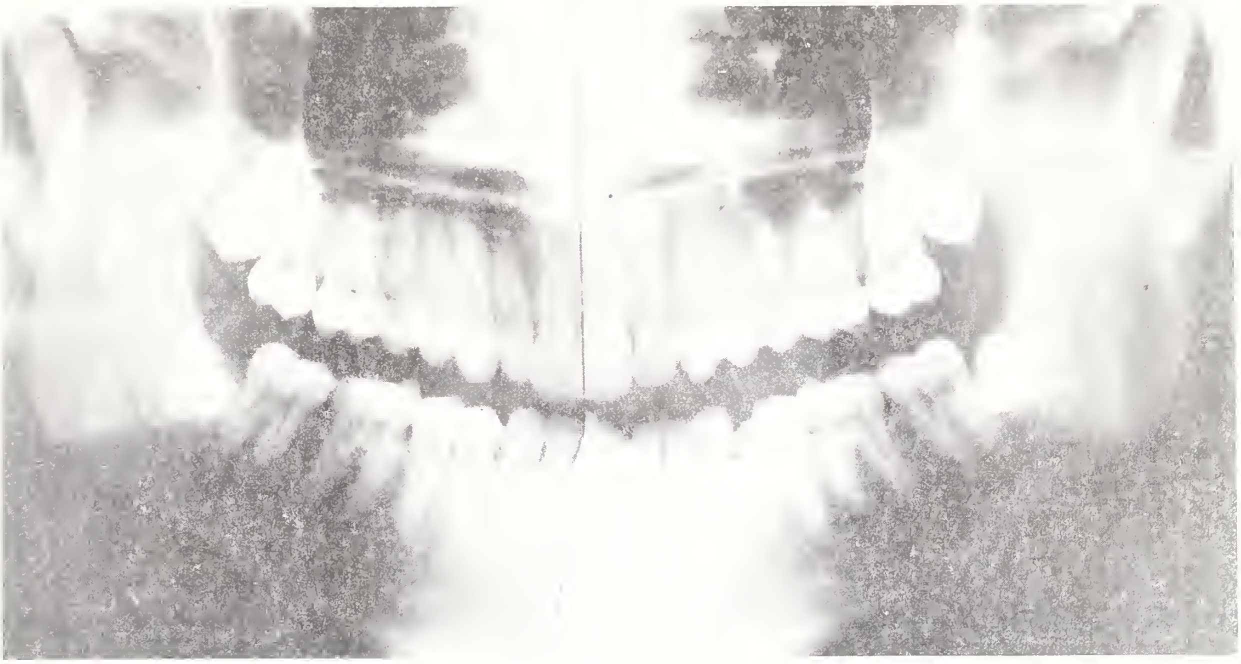

The lower right side of the photo above shows impacted third molar with partial development of root. The lower left side shows impacted third molar with complete root formation closely associated with mandibular nerve. (NIH Photo #1641)

has not been studied and is deserving of prospective investigation.

Although there was no consensus on the subject of removal of asymptomatic impacted teeth with no evidence of pathology, it was agreed that long-range studies of the subject are needed. Consensus was reached that third molars with nonrestorable carious lesions and third molars contributing to resorption of adjacent teeth should be removed.

Finally, there was some concern about the inadequacy of intra-oral radiographs, particularly bite-wings, in assessing third molars. It was decided that the absence of a third molar on a routine dental film, without a history of prior extraction, demands more extensive radiographic examination.

In summary, the conference participants carefully examined the long-established practice of third molar removal. A number of clinical procedures were endorsed; others were controversial but identified as subjects for addi-

(more)

tional research. A number of well-defined criteria for the removal of third molars emerged. They are, in part, infection, nonrestorable carious lesions, cysts, tumors, and destruction of adjacent teeth and bone. There is less morbidity associated with removal of these teeth in the young than in the older patient.

The effectiveness of removal of third molars to prevent crowding of lower incisors is not borne out by the studies currently available. Third molar bud removal in youngsters, based on predictive studies, is not currently an acceptable practice in view of available knowledge.

Clinical experience suggests that morbidity and serious complications may be reduced if impacted teeth are removed at an early age. The observation is not disputed by available data, but there is enough question about the life-cycle of impacted third molars to suggest the need for well-designed prospective studies of the subject.

Co-chairmen for the consensus meeting were Drs. Walter C. Guralnick, Harvard School of Dental Medicine, and Daniel M. Laskin, College of Denistry, University of Illinois. Other members of the Consensus panel were: Drs. Robert Bruce, Adrian, Michigan, Thomas M. Graber, Chicago, Illinois, James Kelly, Bethesda, Maryland, William R. Laney, Rochester, Minnesota, Gilbert Lilly, Iowa City, Iowa, and Alan M. Polson, Rochester, New York.

###

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News&Features FROM NIH

May 1980

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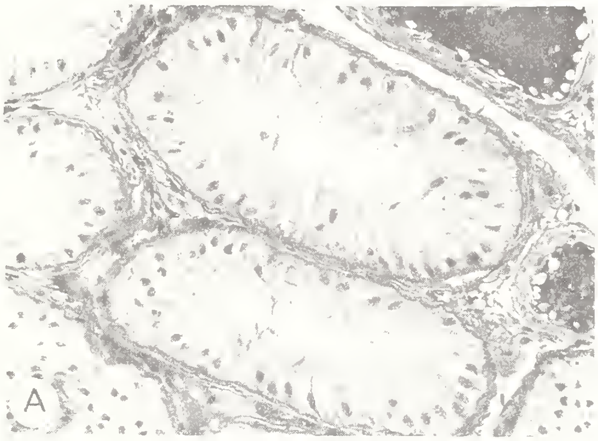

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News & Features
FROM NIH

MOTHER OR SISTER HISTORY OF BREAST CANCER INCREASES RISK

Having either a mother or sister with breast cancer appears to be a strong risk indicator for the disease in other family females. In a study conducted at Harvard Medical School, researchers found that a woman's risk of developing breast cancer was increased by 80 percent if she had a mother with the disease, while having a sister with such a history increased the risk by 150 percent.

Both of these associations were stronger for younger women under age 45 who developed cancer and the risk was still larger for women who had menstruated for more than 35 years.

Female nurses aged 30-55 from the American Nurses' Association participated in the study by filling out a questionnaire on various health-related items, including relevant cancer information.

Seventy-one percent of the nurses completed the questionnaire and 1,159 women recorded a previous hospitalization for breast cancer with a specified date of diagnosis. Ten controls were selected at random from the total group and matched by year of birth to each case. A history of pertinent biologic variables such as menopausal status and previous benign breast disease was taken from the women with a diagnosed case of breast cancer and also from each of the 10 matched controls.

Of the 1,159 cases and 11,590 matched controls, 1,092 cases and 10,620 controls provided complete information on relevant factors. Of these, 9.7 percent of cases and 5.6 percent of the controls reported a positive maternal history of breast cancer. When checking for sister history of the disease, only cases and controls with sisters were included in the analyses for breast cancer risk. Eight percent of 815 cases and 3.4 percent of the 7,808 matched controls had at least one sister with breast cancer. The risk of breast cancer for women

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with no sister was not significantly different from that for women with a sister without the disease.

Drs. C. Bain, F.E. Speizer, B. Rosner, C. Belanger and C.H. Hennekens from Channing Laboratory, in research supported in part by NIH's National Cancer Institute and National Heart, Lung, and Blood Institute, found that the effect of a positive history of breast cancer on a subject's risk of developing the disease appeared more marked among younger women. Ten women younger than 45 years had a positive mother history and sister history of breast cancer. The same 10 women were also premenopausal.

Variables other than age which showed a clear positive association with breast cancer risk were low parity (bearing few children); later age at first birth (defined as a full-term pregnancy lasting 6 or more months) and hospitalization for fibrocystic breast disease or for other benign breast disease.

Of women with a natural menopause, those with late cessation of menses (50 years of age or older) had 2.6 times the risk of those with menopause before age 45. Postmenopausal women had only a slightly higher breast cancer risk than those who were premenopausal. Both of these estimates may be modified as this group of women ages.

Having a mother or a sister with breast cancer appears to be a stronger risk indicator before the menopause than after. However, this finding should be viewed with caution. The association of a positive family history and breast cancer appears to be stronger when there has been no occurence of fibrocystic or other benign breast disease.

The impacts of age at menarche and menopause affect the two risk indicators (mother or sister history) differently, although trend analysis lends little weight to these observations. The effect of the absolute interval between

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menarche and menopause shows that the correlation with maternal history is strongest for those women who menstruate for more than 35 years. There is little or no correlation between sister history and length of menopause.

The reason or reasons why women with close relatives who had breast cancer are more likely to develop the disease themselves is not known. Various causes for the increased risk are thought to be social, dietary or other environmental factors to which particular families are more susceptible.

In findings yet to be published, researchers from the University of California School of Public Health at Berkeley have suggested that breast cancer susceptibility is inherited in some families and the risk is passed on from fathers as well as mothers to their daughters. The suspect gene carries information to make an enzyme known as glutamate-pyruvate transaminase (GPT), which can be detected by looking for its product in a simple blood test. The GPT gene itself may have nothing to do with cancer except to provide a possible marker for the presence of a mysterious gene that increases susceptibility to the disease in certain families.

Information on hormone levels at puberty and from later years taken from daughters of breast cancer cases with varied family histories may also provide some insight into possible modes of transmission through which a familial predisposition to breast cancer may be expressed. The collection of detailed dietary histories about the time of puberty, together with long-term monitoring for outcome may also be of value for breast cancer susceptibility detection.

This article appeared in the *American Journal of Epidemiology*, Vol. 3, No. 3, March issue, and the research was conducted at the Departments of Medicine and Preventive and Social Medicine, Harvard Medical School and Peter Bent Brigham Hospital, Boston, Mass.

###

By Joyce F. McCarthy

PURE PROTEIN DIET MAY BE POTENTIAL HEALTH HAZARD

Man cannot live by meat alone; he needs some bread, too. Recent research has shown the pure protein diet to be a potential health hazard. The addition of carbohydrate to the diet provides the necessary balance.

Results of a study by four physicians at the Yale University School of Medicine show that, compared to a mixed diet containing carbohydrate, a protein diet results in 1) development of a progressive disorder characterized by low blood pressure upon standing (orthostatic hypotension), 2) a decrease in one of the hormones needed to deal with hypotension (norepinephrine), 3) sodium depletion, and 4) decreased function of the sympathetic nervous system.

Many people, eager for rapid weight loss, have tried pure protein diets. The liquid protein diets, which came into popular use in 1977, were, over the next two years, connected with at least 165 reports of adverse reactions. During the same two years, there was a clear correlation between the liquid protein diets, and the deaths (attributed to abnormal heart rhythms) of 16 persons who were using the protein diet as their sole or main source of calories.

As treatment for obesity, protein diets were advocated over mixed diets for two reasons: the supposed advantage of protein diets in conserving body protein, and the belief that patients eating only protein diets stick longer to their diets.

Joseph DeHaven and colleagues say that recent studies comparing protein and mixed diets have been noted either to have been too short (5-10 days) for reliable measure of protein loss, or to have failed to measure protein loss through skin (integumentally) and through stools.

The current study was designed to compare protein loss (through skin, stools and urine) and sodium balance of seven volunteers. Each volunteer

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underwent (for three weeks or longer) the separate hypocaloric (low calorie) diets: a pure protein and a mixed diet. The protein diet consisted of 400 calories per day in the form of boiled turkey. The mixed diet was equi-caloric, consisting of 50 percent protein (boiled turkey) and 50 percent carbohydrate (grape juice). Both diets were supplemented to contain equal amounts of minerals (sodium, potassium, calcium, phosphorus and magnesium). On each test diet, a daily minimum of water (2 liters) was drunk. Exercise was restricted to moderate walking. The order of diets was randomly selected for each volunteer, and between diets, each test subject was placed for two weeks on an interim 2,023 calorie diet, consisting of fat, protein and carbohydrate with mineral supplementation. Six of the seven volunteers underwent each test diet for three weeks; the seventh volunteer stayed on each diet for 5½ weeks, with a 3½ week interim diet. During the entire study, volunteers were housed in the Yale-New Haven Hospital.

Results of the study showed that on the protein diet there was a 20 percent greater weight loss than on the mixed diet (approximately 22 lbs, compared to 17½ lbs, in three weeks); however, the difference was attributed completely to loss of fluid and sodium. (Loss of other minerals did not differ appreciably with the two diets.)

The protein diet offered no advantage over the mixed diet for protein conservation; the amount of protein lost was basically the same on both diets.

The protein diet resulted in excess ketone bodies (a product of fat metabolism) in the blood (hyperketonemia) and in the urine (hyperketonuria). The incidence was two-five times greater on the protein diet than on the mixed diet. (Both hyperketonemia and hyperketonuria are seen in diabetes and in starvation.)

DeHaven and colleagues suggest that the urinary loss of ketone caused by

(more)

the protein diet may partly explain the concommitant loss of sodium. (In turn, sodium depletion may contribute to development of orthostatic hypotension.)

The protein diet also resulted in 40 percent lower basal (resting) levels of norepinephrine in the blood. Norepinephrine is a neurotransmitter (a chemical needed for communication between nerve cells) found in the sympathetic nervous system, and also in the brain (where it is released in response to hypotension.) Moreover, the researchers reported an unexpected observation with the protein diet: in contrast to what would have been expected under conditions of sodium depletion, the plasma levels of norepinephrine did not increase sufficiently when the subject stood up. Based on this, DeHaven and colleagues suggest that the protein diet induces a reduction in sympathetic nervous system activity.

The protein diet also induced orthostatic hypotension, which the authors suggest was caused by a combination of sodium depletion and the decrease in sympathetic nervous system activity. (In orthostatic hypotension, the patient is susceptible to sudden fainting when engaged in activities such as getting out of bed, standing up and taking a shower.)

Having refuted the supposed protein conserving advantage of a pure protein diet, and having documented significant side effects, DeHaven and colleagues point out that no controlled studies have found this diet to promote better adherence or greater long-term weight loss.

This work was supported in part by grants from NIH's National Institute of Arthritis, Metabolism and Digestive Diseases and the Division of Research Resources.

###

By Dinah Bertran

BREATHING DEFECT IN PARENTS LINKED TO SUDDEN INFANT DEATH

A genetic trait of the ventilatory drive system in infants may be a factor in sudden infant death syndrome (SIDS). A recent study has found that parents may be passing on a recessive gene trait which could influence their children's susceptibility to SIDS. The research was supported in part by grants from NIH's Division of Research Resources and National Heart, Lung, and Blood Institute.

SIDS or "crib death" is a phenomenon characterized by the unexplained and unexpected death each year of approximately 10,000 infants and children from one month to one year of age in the United States. Death occurs very rapidly, usually during sleep and there appears to be no suffering. There are about 100 hypotheses to explain the mechanism by which this event occurs (such as suffocation, aspiration or regurgitation), but there now is strong evidence suggesting a defective ventilatory-control mechanism and upper-airway obstruction in SIDS victims.

Apparently there are familial tendencies in the magnitude of the chemical ventilatory drive. Apneic infants (with temporary breathing cessation) or "near miss", and resuscitated by their parents, can be found in familial clusters.

Each of us carries between five and eight recessive genes for serious genetic defects and therefore stand a statistical chance of passing on a serious lethal condition to each child. Genetic diseases are transmitted in essentially three forms: as chromosomal abnormalities, as single-gene defects, and as complex disorders resulting from the combined action of multiple genes and/or environmental factors.

In recessive inheritance both parents, usually unaffected, carry a normal

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gene (N) which takes precedence over its faulty recessive counterpart (n). The odds for each child's inheritance are: a 25 percent risk of inheriting a "double dose" of n genes which may cause a serious birth defect; a 25 percent chance of inheriting two Ns, thus being free of the recessive gene, and a 50 percent chance of being a carrier like both parents. In this study, it appears that the parent and/or parents of SIDS victims are affected by a multigenic trait which may be coupling and transmitted to the children in the expression of a ventilatory disorder.

Researchers from Rutgers Medical School tested parents of SIDS victims for two important aspects of ventilatory control used in the defense response to partial airway obstruction. These were the ventilatory response to carbon dioxide and the compensatory response to a flow-resistive load. The compensatory response is increased inspiration due to either pathologic or experimentally induced acute increases in resistance to breathing.

Six couples (12 parents) of SIDS victims and six couples with no SIDS history in their families were studied. The control group was matched with the test group for age, body size and sex. All persons tested in each group were without history of cardiac or pulmonary diseases and had normal lung vital capacities (the greatest volume of air the lungs can breathe out). About 25 percent of each group were cigarette smokers.

All subjects were seated and rebreathed a mixture of five percent carbon dioxide in oxygen for approximately four minutes through a mouthpiece attached to a half-filled, 13-liter balloon with a one-way valve. An inspiratory flow-resistive load was added in random sequence to one of the tests. This degree of resistance was chosen because prior testing had indicated that virtually all normal subjects manifested respiratory compensation to it.

The valve on the inspiratory line was closed during an exhalation of 20-30

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second intervals so that the subject would breathe against complete occulsion at the start of the subsequent inhalation. The valve was closed for one breath only, did not interfere with exhalation and was shielded from the subjects so that they would not predict when an occlusion would occur.

The results show that parents of SIDS victims had significantly lower ventilatory responses to carbon dioxide than did the matched controls. As a group, parents of SIDS victims were likely to be drawn from that portion of the population who are relatively unresponsive to carbon dioxide as a ventilatory stimulus.

Evidence is mounting that when persons with low responsiveness to carbon dioxide are presented with mechanical burdens to breathing such as obesity, asthma and chronic bronchitis, they are more apt to manifest alveolar hypoventilation than subjects who are more responsive to carbon dioxide. Therefore, hyporesponsiveness to carbon dioxide is probably best considered a "risk factor" in the pathogenesis of SIDS.

The addition of a sufficiently large mechanical impairment to breathing will cause a decrease in a normal subject's ventilatory response to carbon dioxide. Normal subjects have shown that the higher the resistance, the greater the likelihood of the compensatory response. The normal response was confirmed by the control group. In contrast, as a group, the parents of SIDS victims did not manifest this compensatory response and the control group's response was five times that of the SIDS parents. Most partners of each SIDS couple studied had either no response or abnormally low responses to an acute increase in airway resistance.

Within the general population there is a wide range of ventilatory responsiveness to carbon dioxide. Such a distribution is consistent with a polygenic trait. If the ventilatory response to carbon dioxide is polygenic in nature,

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the chances of an infant manifesting an extremely low response would, of course, be greatest if both parents were low responders. It is also possible that the familial clustering of low ventilatory responses to carbon dioxide is determined by a separate autosomal-recessive gene.

An infant with both low ventilatory responsiveness to carbon dioxide and low responsiveness to flow-resistive loads would be substantially more likely than the average infant to hypoventilate in the presence of an acute increase in resistance to airflow. This could occur at a susceptible age during an upper-respiratory-tract infection, on a positional basis, due to inappropriate upper-airway muscular relaxation or constriction during sleep, or due to other factors.

The study concludes that potential parents who exhibit a low ventilatory response to carbon dioxide and a low response to flow-resistive loads may be at increased risk to have children susceptible to SIDS.

This research was conducted by Drs. Philip L. Schiffman, Robert E. Westlake, Teodoro V. Santiago and Norman H. Edelman, College of Medicine and Dentistry of New Jersey, Rutgers Medical School, Piscataway, N.J. The article appeared in *The New England Journal of Medicine,* Feb. 28, 1980, Vol. 302, No. 9, p. 486.

###

By Joyce F. McCarthy

MAMMALIAN AND PARASITE DNA JOINED BY CELL FUSION

The successful union of parasite and mammalian DNA has been demonstrated for the first time by scientists using a technique known as cell fusion at NIH's National Institute of Allergy and Infectious Diseases (NIAID). Hybrid cells expressing parasite antigen have been grown from this unusual coupling. According to the investigators, this method of producing parasite antigen may be useful for studying parasite diseases, and possibly for developing vaccines.

The hybrids were formed by fusing the parasite that causes Chagas' disease, *Trypanosoma cruzi, (T. cruzi)* with standard laboratory-grown bovine embryos and mice cells.

At present, there is no effective method for controlling Chagas' disease--a major public health problem in Central and South America, and affecting an estimated 12 to 20 million individuals. The parasite is transmitted by blood-sucking insects that are frequently found in poorly constructed adobe houses. There is no reliable treatment for the disease, and it can often lead to severe debilitation and death.

Insect eradication is extremely costly to pursue on a large-scale basis needed for control of the disease throughout the continent. Furthermore, experimental vaccines prepared from either whole living or dead organisms or fractions of the parasite have produced only a limited immunity to infection. This can be partially explained by the fact that during the body's immune response to the parasite, some of the antibodies produced may actually be harmful rather than protective.

If a noninfectious antigen that stimulates protective antibody could be isolated and produced, vaccine development might be possible. Since isolating, purifying and characterizing *T. cruzi* antigen like other parasitic antigens

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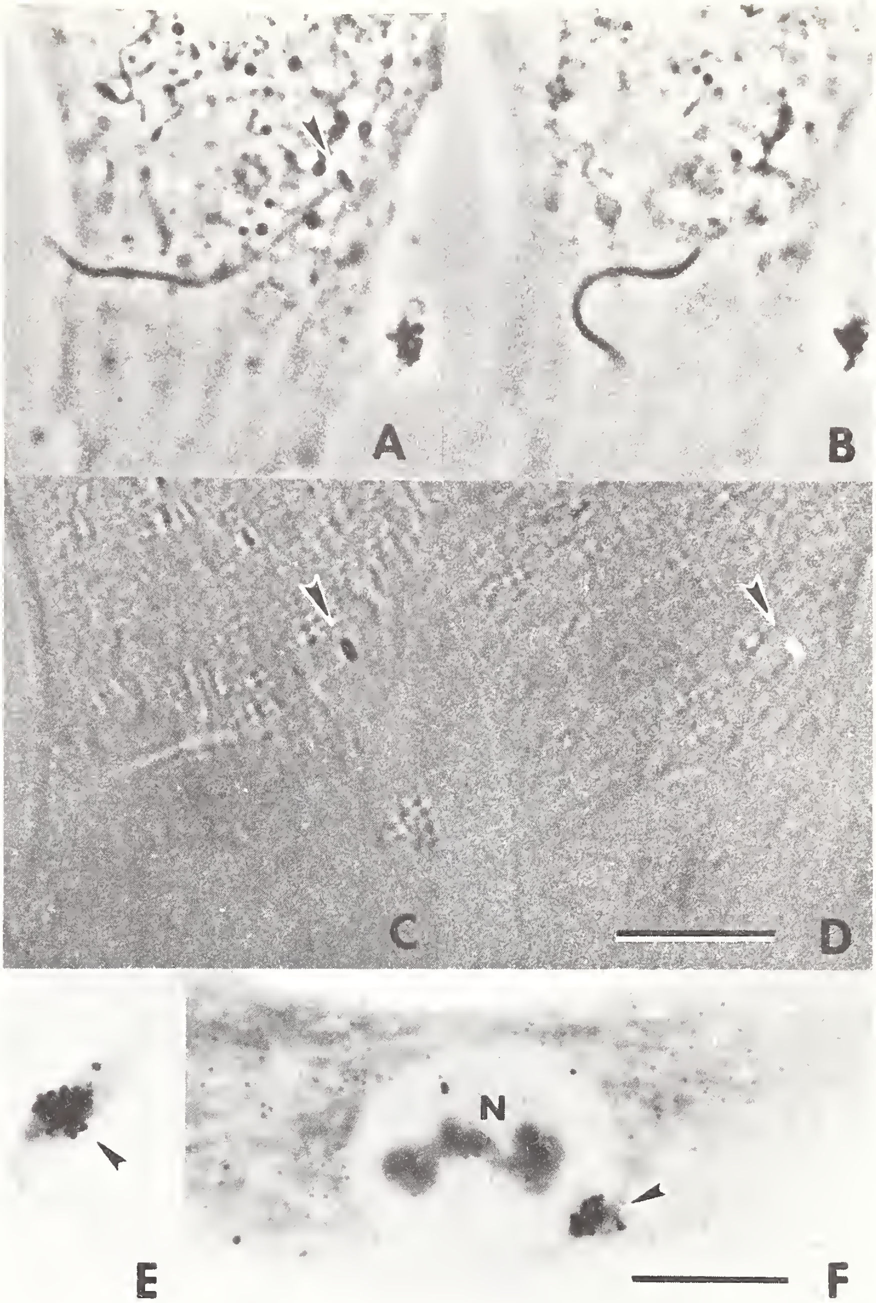
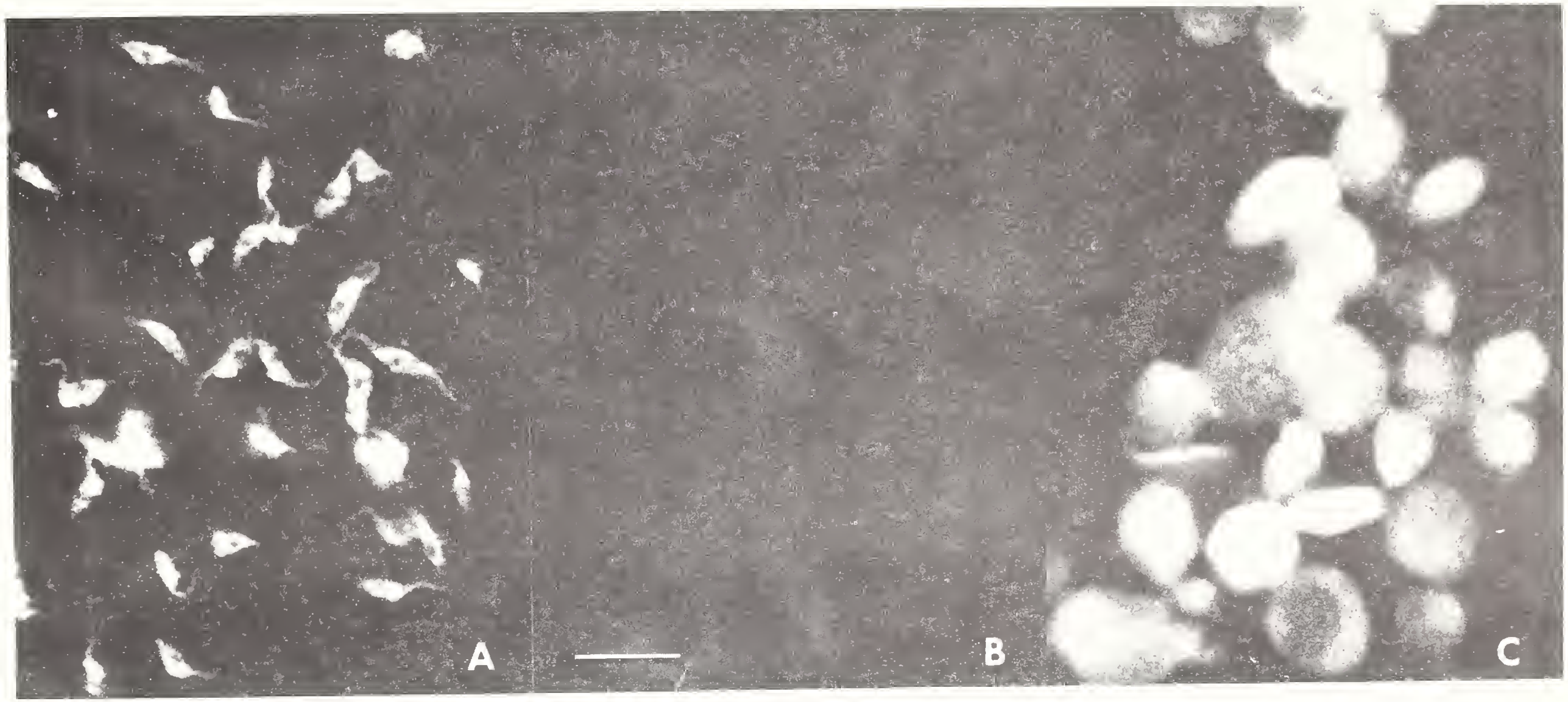


Phase-contrast photomicrographs show bovine embryo cells combined with T. cruzi (A and B) after treatment with the chemical, polyethyleneglycol. These pictures were taken approximately 20 minutes after treatment with the chemical and show the fusion of the two cells. Figure B shows the parasite flagellum extending from the fused cell. Figures C and D are the same photo but contrasted by polarized light showing the parasite kinetoplast (extra-nuclear body associated with the flagellum). Figures E and F show a single T. cruzi parasite cell with labeled nucleus. Photo at right, taken 24 hours after the parasite and mammalian cell were chemically united, demonstrates the presence of the parasite nucleus inside the mammalian cell. (NIH Photo #1642)



The NIAID scientists used a technique known as indirect immunofluorescent antibody assay to test for the presence of parasite antigen in the hybrid cells. This was done by incubating them with antibodies labeled with a fluorescent dye that allows parasite antigen to be visualized. If antigen is present, the cells absorb the stain and appear in the photo. Photo A shows fluorescent-stained parasite cells, while in photo B mouse cells do not pick up the stain. Hybrids that express antigen appear in photo C. (NIH Photo #1643)

has been difficult, NIAID researchers have been exploring new methods for producing parasite antigen such as cell fusion.

In the reported study, the NIAID investigators took the insect stage of the parasite and chemically fused it with mammalian cells. Hybrids were grown in a selection medium and tested for the presence of *T. cruzi* antigen, through a process known as indirect immunofluorescent antibody assay.

The investigators found that three hybrid cell cultures expressed antigen specific for *T. cruzi*. Since none of the cultures were actually infected, antigen expression could not be attributed to the presence of parasites.

How the *T. cruzi* genetic material is incorporated into the vertebrate cell nucleus is not known. *T. cruzi* nuclear DNA is not organized into chromosomes, typical of mammalian cells, so it cannot be analyzed by conventional methods. Nonetheless, the investigators believe that the detection of *T. cruzi* antigen several weeks after fusion indicates the presence of functional parasite DNA.

The NIAID scientists speculate that several applications may arise from this research. Producing selected antigens may be useful in studying the disease process in Chagas' disease and in improving already existing immunodiagnostic tests. If any of the antigens are shown to induce only protective antibodies in animals, for instance, then it may be possible to develop a vaccine.

According to the authors, their study is the first reported successful fusion and hybrid formation between vertebrate and invertebrate cells. They believe that fusion may be possible in other parasite-mammalian systems as well, and may be a useful technique for investigating a number of other, poorly understood parasitic infectious diseases.

(more)

The report of this research by Mark St. J. Crane and James A. Dvorak, from NIH's NIAID Laboratory of Parasitic Diseases, appeared in the April 11, 1980 issue of *Science*, Vol. 28, No. 4,400, pg. 194.

###

By Mary Donovan

SEXUAL FUNCTION LOSS TIED TO ALCOHOL ABUSE

Many men may be making themselves impotent, sterile and more feminized by chronic alcohol abuse, according to a recent report by NIH's Division of Research Resources.

While it is difficult to identify the amount of alcohol consumed that will cause sexual function loss, Dr. David Van Thiel, associate professor of medicine at the School of Medicine, University of Pittsburgh, is certain that these problems are not restricted to skid row or end-stage alcoholics. The early signs of alcohol damage to the reproductive system can appear after a single binge.

Studies conducted at DRR's General Clinical Research Center of the Presbyterian-University Hospital in Pittsburgh show that drinking enough alcohol to cause a hangover can decrease testosterone (key male sex hormone) levels in normal, healthy men who may be occasional drinkers. Dr. Van Thiel finds symptoms of alcohol abuse in many young men complaining of infertility.

About 9 million adult Americans are alcoholics and most appear to function normally, however, sexual dysfunction is a major problem and can occur at a comparatively young age. Drinking an average of a pint or more of hard liquor per day for five to eight years may cause loss of sexual function entirely, suggests Dr. Van Thiel.

Seventy to 80 percent of male alcoholics suffer decreased libido, impotence and sterility. These effects of chronic drinking may persist between intervals of drinking and possibly after the alcoholic completely "dries out."

Although many men may regain some sexual function if they stop consuming liquor, for others the damage may be irreversible. The clinical researchers in Pittsburgh believe they have determined, in part, the process by which alcohol upsets normal function.

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Previously, scientists thought that sexual dysfunction resulted indirectly from alcohol-induced liver damage, but, according to Dr. Van Thiel's six-year study, alcohol directly damages the gonads (primary sex glands) and parts of the brain. Specifically, it seems to damage sections of the hypothalamus and pituitary that control the function of the testes. The hypothalamus produces a series of hormones, or peptides, that stimulate the pituitary which, in turn, releases two hormones (LH, luteinizing hormone, and FSH, follicle stimulating hormone).

In males, these two important hormones stimultate the testes to produce testosterone and sperm. Any disruption results in varying degrees of sexual or reproductive function loss. A low sperm count makes men sterile, and their low testosterone levels may make them impotent and decrease their sex drive. Chronic alcohol abuse also makes men appear more feminine. Alcoholic men may exhibit changes in secondary sex characteristics, such as redistribution of hair and fat to patterns more like those of females.

The Pittsburgh investigators have researched the biochemical mechanism by which this occurs: a combination of reduced testosterone levels and increased estrogen levels. Dr. Van Thiel says that alcoholic men have increased estrogen levels in peripheral cells -- for instance, in their breasts. One of the most important aspects of the study, he believes, is that infertility caused by alcohol abuse can now be diagnosed early. No elaborate tests are necessary, he says.

If infertility due to alcohol can be diagnosed early, sexual functions may improve. Regardless of the extent of the damage, the best treatment for the problem, according to Dr. Van Thiel, is to stop drinking.

There is no other current therapy of proved value. He believes that the effects of alcohol on sexuality may be additional persuasive evidence for

(more)

patient education in the prevention of alcohol abuse. The studies in Pittsburgh were supported by the National Institute on Alcohol Abuse and Alcoholism, the Distilled Spirits Council of the United States, Inc., and the General Clinical Research Centers Program of DRR.

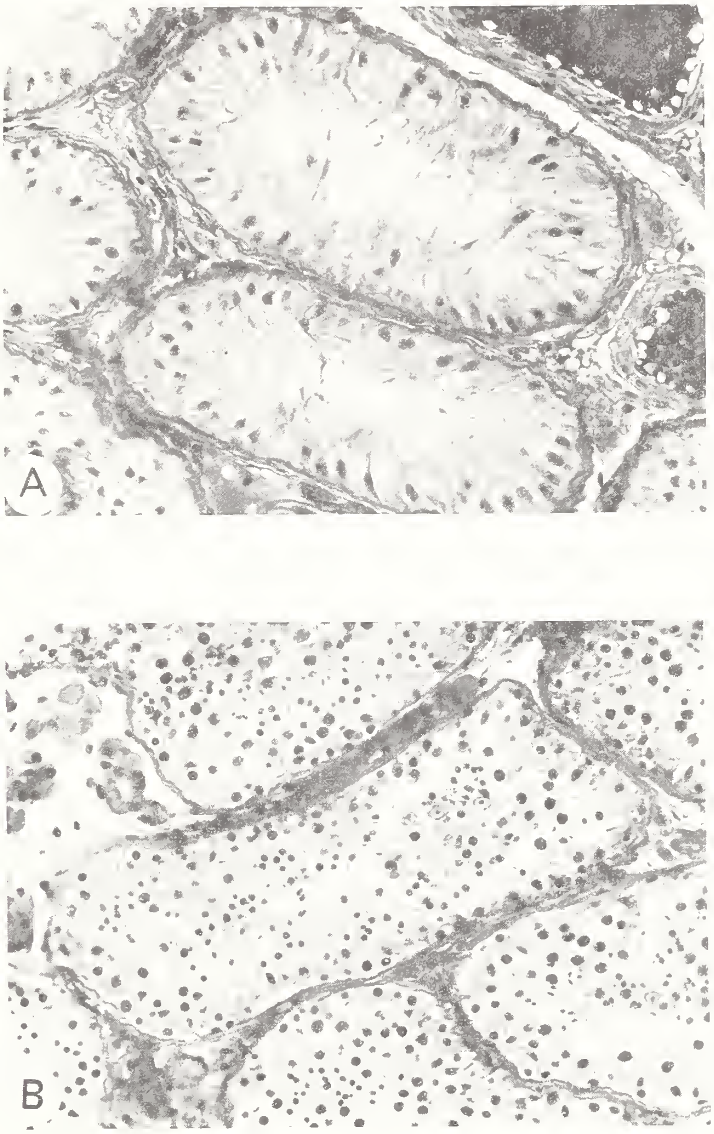

Figure A shows severe germ cell damage in the testes affected by chronic alcohol abuse. The affected cells can be easily distinguished from normal testes cells shown in Figure B.
(NIH Photo #1644)
(NIH Photo #1645)

###

NIGERIA AND NIH JOIN IN NEUROLOGICAL STUDY

Do West Africans have as many strokes as American blacks? Is hypertension as great a risk factor for stroke in West Africa as it is in the United States? Is Parkinson's disease--a relatively uncommon disorder among American blacks--a significant health problem in West Africa?

To help answer these and other questions, scientists from NIH's National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) are collaborating with West African colleagues to develop protocols for the first epidemiological studies of neurological disorders in Nigeria. The data will help the Nigerian government set priorities for prevention and treatment programs.

Cerebrovascular disorders, such as stroke, will be studied as well as extrapyramidal disorders, such as Parkinson's disease. Data also will be collected and analyzed on peripheral neuropathies and convulsive disorders. This pilot project is intended to serve as a model for epidemiological studies elsewhere. Its progress is being closely followed by many developing countries and the World Health Organization.

Dr. Benjamin Osuntokun, professor of neurology at the University of Ibaden, Nigeria, is working on the pilot project with Dr. Bruce Schoenberg, chief of the NINCDS neuroepidemiology section. Within the next year, representatives from other countries interested in using the protocols will participate in a special two-week course on neuroepidemiology and will observe actual survey procedures in Nigeria.

Collecting epidemiological data in developing countries poses special problems. In Nigeria, about 60 percent of people needing health care go first to native herb doctors and then to modern medical practitioners when they find they are not getting any better. By the time Dr. Osuntokun and his colleagues

(more)

see patients, it is often too late to learn much about prior events in an illness. In addition, the cause of death for many Nigerians is not recorded--greatly complicating the process of compiling accurate data.

Lay health workers will play key roles in gathering data for the new study. They will interview people, collect answers on a questionnaire and conduct a simple examination of patients. Anyone suspected of having neurological problems will be referred to a neurologist for diagnosis and treatment.

The study will include an effort to gather data on an important Nigerian health problem: cassava poisoning. The extremely hardy cassava shrub, which can grow as high as 10 feet, was introduced to Nigeria in the late 19th century by former slaves returning from Brazil.

Cassava, any of several plants of the genus *manihot* is eaten as tapioca in the United States. It is prepared by heating the roots of the plant while moist. It is a major source of carbohydrate for Nigerians as well as nearly 300 million people around the world. Proper preparation of cassava's fleshy tubers includes a two-week fermentation. If improperly prepared, cassava has a high cyanide content.

Whole families have been wiped out from a single meal of improperly prepared cassava. Chronic degenerative neuropathies leading to blindness, deafness and crippling are also common among those whose diets are high in cassava and low in protein.

The Nigerian-NINCDS study will help to determine the frequency of death and debility due to cassava poisoning in the population. The data-gathering phase of the Nigerian pilot project will begin in May or June, and the data will be processed by neuroepidemiologists at the NIH campus in Bethesda, Md.

###

By Doris Parker

EXPERIMENTS REVEAL OBESE MICE ARE ENERGY-EFFICIENT THERMOREGULATORS

Eating a high-fat diet and being obese may not be all that bad. In times of famine, it may give a survival advantage--at least if you are a mouse.

Experiments comparing genetically obese mice with lean mice have suggested that, on a high-fat diet, obese mice use energy (the food they eat) more efficiently. They can survive on less food, and store more energy for future use. What mixes the blessing is that they also lose some ability to survive cold.

Obesity in certain mice is inherited (genetic). This may have significant implications, because the ability of obese mice to use energy more efficiently may be inherited along with the genes for obesity. Whether obesity is hereditary in humans is not clearly known.

A study by Jerry G. Vander Tuig and colleagues, from Michigan State University, suggests that the greater energy efficiency may be due in part to a difference in the way the mouse's thermostat (thermoregulatory system) works.

The authors had noted in an earlier study that at temperatures which are below the level of thermoneutrality for mice, obese mice needed 40 percent less maintenance energy than did lean mice. (Thermoneutrality is the environmental temperature at which the body will not have to burn any of its stored energy--its fat and protein--to stay warm.) They concluded that the obese mice used the food they ate more efficiently, so they needed less--even at the cooler environmental temperatures which ordinarily would have made the thermoregulatory system prompt the body to take in more food.

Since there is less need for heat production at the thermoneutral temperature, a thermoregulatory difference would be indicated if the obese mice were as energy efficient at the thermoneutral temperature as they were at the cooler temperatures. For this reason, mice in the current study were kept in a room

(more)

where the temperature was approximately thermoneutral for mice (33° C, or 91.4° F).

The current study consisted of two groups of young female mice: genetically obese and lean. Both groups were divided into six sub-groups to test two variables: type of diet and quantity of food eaten.

Diets were either high-fat or high-carbohydrate. Mice in the two diet groups were further divided into three groups, according to how much they were allowed to eat: ad libitum (as much as desired), 75 percent and 50 percent (of the average ad libitum amount eaten by lean mice).

The results of the study showed the high-fat diet to be more conducive to energy efficiency: both obese and lean mice stored more energy on the high-fat diet than they did on the high-carbohydrate diet. This observation is in accord with a previous study by the authors.

However, obese mice fed the high-fat diet ad libitum were significantly more efficient than were lean mice on the same diet. (Obese mice stored three times as much energy. They also gained twice as much weight.) Also, in every group, obese mice stored more energy than did lean mice.

There was another difference between obese and lean mice, namely, in the form in which energy was stored. Obese mice allowed to eat freely of the high-fat diet stored most of the energy as fat, rather than as protein. By comparison, lean mice tended to store more energy as protein.

Because fat needs less energy to store and to burn, the body with the most fat will have a survival advantage in times of starvation.

The authors state that if a thermoregulatory difference were entirely responsible for the energy efficiency of obese mice, then both the obese and the lean mice should need the same amount of maintenance energy at the thermoneutral temperature.

Such was not the case, however. In the current study, obese mice still

(more)

needed less maintenance energy than did lean mice. The lean mice became more energy efficient at the thermoneutral versus the cooler temperature, whereas the obese mice maintained the same rate of efficiency in spite of the warmer environment of thermoneutrality. Tuig and colleagues concluded that a thermoregulatory difference only partly explains the energy efficiency of obese mice.

The authors suggest that, in addition to thermoregulation, other factors, still undefined, will provide a fuller explanation. Some of these factors may be the lower body temperature and the increased efficiency of oxygen utilization of the obese mice. Tuig and colleagues also suggest further research to explain why a high-fat diet is a more efficient source of energy than a high-carbohydrate diet.

The study was supported in part by a grant from the National Institute of Arthritis, Metabolism and Digestive Diseases, and was reported in the January issue of the *Journal of Nutrition*.

###

By Dinah Bertran

SEXUALLY TRANSMITTED DISEASES AFFECT ONE-IN-20 AMERICANS

A recent meeting of the Sexually Transmitted Diseases (STD) Study Group of NIH's National Institute of Allergy and Infectious Diseases brought together international experts to review current problems and determine new research needs and directions.

STDs affect at least one American in 20 each year, causing problems ranging from local discomfort to chronic disabling disease, infertility, ectopic pregnancy, stillbirth and neonatal death. Most are easily treatable and all but one, herpesvirus, curable. Gonorrhea affects an estimated 2 million Americans each year. Three million have nongonococcal urethritis or cervicitis caused by *Chlamydia trachomatis*, *Ureaplasma urealyticum*, or other unknown pathogens. Another 3 million get trichomoniasis, and 400,000 a year have syphilis. Genital herpesvirus (HSV) infections, which already afflict more than 5 million Americans and can last for life, claim as many as 500,000 new victims each year.

Researchers in the field are unanimous in predicting a rising annual STD toll in the coming years. There are several possible factors in the steady increase of STDs. First, the rising number of sexually active adults and adolescents, some of whom are becoming sexually active at an early age and who have several sexual partners. Second, practicing physicians who are not knowledgeable about the new generation of diseases and how to treat the symptoms or their patients' contacts. Both of these reasons are helping to fuel the epidemic.

Dr. King K. Holmes, who chaired the meeting, is associate professor of medicine, University of Washington, and chief, division of infectious diseases, PHS Hospital, Seattle. He has reported that sexually transmitted *Chlamydia*

(more)

diseases are rapidly overtaking gonorrhea as the nation's No. 1 STD. He stated that there is a need for both rational guidelines for screening and management of STDs and for rapid, accurate and inexpensive screening tests. There is no standard practice or recommendation for routine gonorrhea screening of asymptomatic but high-risk, sexually active women, for whom the diagnosis requires cultures.

The STD study group concluded that additional basic research is urgently needed for all sexually transmitted diseases. They recommended that an accelerated training program be developed to increase the staffing of STD experts in public health and VD clinics as well as in medical schools and schools of public health. Dr. Richard Krause, director of the NIAID, hopes to persuade medical school deans to launch training programs in the new venerealogy in the hope of meeting the institute's projected need for 200 new clinicians each year for the next 10 years.

The development of a vaccine for the treatment of gonorrhea is of major importance and so is additional research on genital herpes, for which there is presently no satisfactory treatment.

The study group also recommended additional funding for syphilis research with continued emphasis on culturing the causative organism, the inclusion of group B streptococci in all general studies of STD because of its emergence as a major pathogen among newborns; more studies on the basic biology and immunology of *Chlamydia* and the development of improved diagnostic methods needed to control *Chlamydia* infections, which affect more than 3 million Americans each year, and increased research on vaginitis, a disorder that general practitioners consistently rank as among the 10 most frequently encountered.

Scientists have determined that certain patterns of sexual behavior may

(more)

favor the spread of hepatitis B, and may be implicated in hepatitis A as well as non-A, non-B. The group recommended that more detailed epidemiologic and experimental studies be undertaken to determine the exact role of sexual transmission in viral hepatitis.

Additionally, scientists recommend that better forms of therapy be developed to treat special STD problems, such as enteric infections, chancroid, ectoparasites and genital warts.

Dr. Lars Westrom (left) from the University Hospital, Lund, Sweden meets with Dr. King K. Holmes, chairman of the meeting, from the University of Washington, PHS Hospital, Seattle. (NIH Photo #1646)

###

CONSENSUS DEVELOPMENT MEETING SET ON MANAGEMENT OF FEBRILE SEIZURES

One out of every 28 children in the United States will have a seizure associated with fever before the age of 7 years. These "febrile seizures" are the most common type of convulsion in young children.

The risks facing these children, and the long-term medical care that such children may require will be the subjects of a consensus development conference to be held at the National Institutes of Health, May 19-21.

The conference is sponsored by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), which has primary responsibility for research on the brain and central nervous system.

Experts in neurology, pediatrics, pediatric neurology, family practice, epidemiology and the social sciences will review what is known about the nature and consequences of febrile seizures and attempt to reach consensus on which of available methods are the best for managing children with this medical problem.

Specific questions to be discussed include: Can long-term or intermittent treatment reduce risks to children who have fever-related seizures? Which children should be considered for treatment? Can we now develop a rational approach to managing these children, or are further studies needed?

Sessions begin at 8:30 a.m. Monday, May 19, in the Masur Auditorium, NIH Clinical Center (Building 10), Bethesda, Md. Participants will first define febrile seizures, and then consider whether children with febrile seizures are more likely than other children to develop additional serious problems, such as epilepsy, mental retardation, cerebral palsy or learning disabilities.

In the afternoon, participants will review how U.S. physicians provide care for children who have had febrile seizures, concentrating on the goals of

(more)

treatment and the criteria used for referring children to a neurologist. The views of a child neurologist and a community-based general practitioner will be heard, and the role of family support examined.

At 8:30 a.m. Tuesday, May 20, participants will begin discussing drug treatment of febrile seizures, including how anticonvulsant drugs might affect a young child's behavior and development.

Tuesday afternoon, the need for further clinical research will be considered, followed by a discussion of public policy issues of special interest to parents and consumers. Brief presentations will be made by individuals and representatives of organizations concerned with children's health.

Panel members will present their recommendations to the consensus conference Wednesday, May 21, at 9 a.m.

A press conference with panel members will be held at noon Wednesday.

Program chairpersons for the conference, titled "Long-Term Management of Children with Febrile Seizures," are Karin B. Nelson, M.D., chief, cerebral palsy and other motor disorders section, NINCDS, and Jonas H. Ellenberg, Ph.D., chief, section on mathematical statistics, NINCDS.

Other NIH units helping to organize the conference are the National Institute of Child Health and Human Development and the Office for Medical Applications of Research.

NIH sponsors consensus development conferences to bring together biomedical research scientists, practicing physicians, allied health care providers and consumers to assess the safety and effectiveness of selected medical technologies, treatments and procedures.

###

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October 1980

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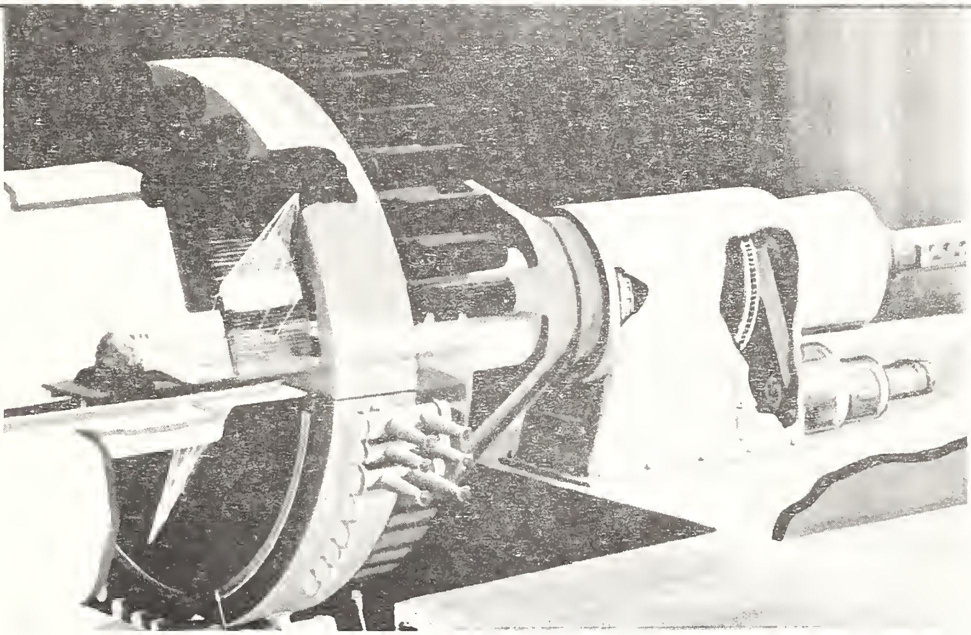

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News&Features
FROM NIH

LEAD POISONING DETECTED IN WEALTHY ADULTS

By Thomas Hawkins

Lead poisoning, usually associated with small children living in slum dwellings who have eaten lead paint chips from decaying ceilings and walls, has been found in an entirely different and unexpected population.

Researchers at the Environmental Health Sciences Laboratory at Mt. Sinai Hospital in New York City have detected cases of lead poisoning in prosperous adults. This newly defined group of lead poisoning victims encounters lead dust and fumes not as a result of hardship and deprivation, but in the course of what they find a pleasurable pastime -- in the preservation and restoration of old buildings and homes, often their own residences. Here, in the process of stripping coats of old lead paint from interior walls, ceilings and woodwork, prosperous young professionals have fallen prey to poisoning, usually associated with the poor.

Dr. Alf Fischbein of the Mt. Sinai Center points out that there is virtually nothing about this form of lead poisoning that matches the textbooks or what has generally been published. These new lead poisoning victims often present none of the classic symptoms, no weakness in the wrists, no colic, no constipation, no lead lines in the gums. In fact, the symptoms are often mistakenly attributed to abdominal disorders, overwork, stress or fatigue.

Fischbein cites a particular patient, as an example of this phenomenon, who recovered sufficiently after the first symptoms to resume his house restoration work. The early symptoms were dismissed as the result of heat, fatigue and hurried eating habits. Later, when the patient suggested the possibility of lead poisoning to an internist, it was waved aside because the symptoms were not characteristic. For example, instead of the constipation usually associated with lead poisoning, the patient had bouts of severe

(more)

diarrhea. Instead of the diminished appetite, he went on eating but lost ten pounds.

At his own insistance, the patient was given a blood test which revealed elevated blood lead levels, resulting in treatment for the poisoning.

Fischbein said that physicians not used to treating lead poisoning may not know that acceptable blood lead levels have been lowered recently from 80 micrograms per hundred milliliters to 40 for men and 30 for women, with some opinion that they should be lower still. Indeed, blood level is not the entire story since lead can accumulate in various organs and may cause poisoning while blood levels are "safe." Doctors should ask questions to reveal lead exposures and use urine samples in diagnosing possible lead poisoning.

This study conducted at Mt. Sinai Hospital was sponsored in part by the National Institute of Environmental Health Sciences, Research Triangle Park, N.C.

###

News & Features FROM NIH

NIH STUDIES INFANTS FED WITH SOYBEAN-BASED FORMULAS

By Thomas Flavin

The National Institutes of Health have begun a five-year, follow-up study of infants who were fed one of two soybean-based formulas deficient in chloride, an essential nutrient. The formulas have been implicated in growth and developmental problems and blood abnormalities.

A team of NIH investigators will conduct the study under the leadership of Dr. Van S. Hubbard of the National Institute of Arthritis, Metabolism and Digestive Diseases, Pediatric Metabolism Branch.

During the first phase of the study, physicians will evaluate the infants' current physical and developmental status to provide a basis for future comparisons. Periodic re-evaluations should then reveal any long-term effects on growth and development of the hypokalemic (low-potassium) metabolic alkalosis that resulted from the formulas. Metabolic alkalosis is an accumulation in the body of organic base compounds, such as blood bicarbonate, resulting in a derangement of the normal acid-base balance.

In July 1979 a kidney specialist reported three cases of metabolic alkalosis in infants who were being fed only Neo-Mull-Soy, one of the soy formulas. Further investigation found 118 cases of infants who had at least one episode of metabolic alkalosis while being fed Neo-Mull-Soy or CHO-Free, the other formula.

Analysis of formula preparations found that the products were improperly manufactured so that they contained one-third the chloride stated on the product label and supplied approximately one-fifth the chloride recommended for infants by the American Academy of Pediatrics. The formulas were voluntarily recalled after having been on the market for about 16 months.

Infants who were fed either Neo-Mull-Soy or CHO-Free will be admitted to

(more)

the NIH Clinical Center as either in-patients or out-patients upon referral by their private pediatricians. Because all the infants will be less than two years old at the time of enrollment, consent from at least one parent will be obtained before diagnostic tests are performed. Researchers will record medical, social, and dietary histories and conduct complete physical examinations of the infants. Diagnostic studies will screen for metabolic abnormalities and delayed growth and development.

A few infants were studied by their own physicians during the most-severe phase of their illness. These infants will be admitted as in-patients for two weeks to determine how they respond to a low, but adequate, sodium level in their diet. Investigators will also take special measurements to detect possible hormonal changes. None of the diagnostic tests will harm the infants, and if any abnormalities are found, they will be further evaluated and treated.

Because only about 1 percent of the infants receiving the formulas developed hypokalemic metabolic alkalosis, the study will try to determine if certain infants have a naturally higher risk of developing metabolic abnormalities during low chloride intake.

The studies have been selected in order to rule out other causes of metabolic alkalosis, especially Bartter's Syndrome, which has symptoms similar to those observed in these infants. Dr. Frederick C. Bartter, who discovered the syndrome, will serve as a consultant to the NIH investigators.

Dr. Jose Cordero of the Bureau of Epidemiology of the Center for Disease Control and Dr. Allan L. Forbes of the Food and Drug Administration will also serve as consultants for the study.

The study, established at the recommendation of the NIH Nutrition Coordinating Committee Office, will include four associate investigators. These are: Dr. James W. Hansen of the National Institute of Child Health and Human

(more)

Development; Dr. Artemis P. Simopoulos, chairman of the NIH Nutrition Coordinating Committee, Office of the Director; Dr. Charles C.C. Chang of the National Institute of Neurological and Communicative Disorders and Stroke; and Dr. Howard A. Moss of the National Institute of Mental Health, another agency in the Public Health Service.

###

News & Features
FROM NIH

COMPUTERIZED X-RAY MACHINE PICTURES ORGANS IN ACTION

By William Glitz

Researchers at the Mayo Clinic in Rochester, Minn., recently demonstrated a new x-ray machine that allows biomedical scientists to view the heart, lungs and large vessels in three-dimensional motion.

This new research tool, called the Dynamic Spatial Reconstructor (DSR) may aid investigators in better comprehending the physiology of the cardiovascular system.

Under a grant supported by NIH, the DSR was developed by a team of multidisciplinary investigators in the Biodynamics Research Unit at Mayo Clinic. Dr. Earl Wood, a pioneer in the study of heart and circulatory physiology, helped launch the DSR effort seven years ago. According to Wood, investigators using this complex computer-based system can now observe congenital heart defects or investigate the extent of muscle damage that may occur after a heart attack. Researchers will also be able to detect and investigate coronary artery narrowing and watch changes in the blood supply to the heart. Such disorders as rheumatic heart disease and cardiomyopathies, disorders of the heart muscle, can also be observed with the use of DSR.

According to Wood, the capabilities of the DSR go beyond the current generation of x-ray scanning devices such as the CAT scanners which only produce single static images of internal organs. The DSR should prove effective for investigating the structure and function of the heart, lungs and circulation because it operates at such a high speed to show a complete picture of body organs in motion. A three-dimensional viewing of the organ from all angles gives the researcher a detailed image of the organ's internal structure.

The DSR is designed with 14 x-ray tubes positioned on a circular structure which rotates around the patient. The x-ray tubes can be turned on and off

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quickly so that 14 different views can be obtained in one-hundredth of a second and repeated as often as 60 times per second. These x-ray angles are then converted to electronic form by special video cameras and stored on video discs similar to those used in instant replays of televised athletic events.

According to Dr. Erik Ritman, a physiologist who heads up the Biodynamics Research Unit, when an investigator wishes to look at any section of the body that has been x-rayed by the DSR, the desired computer-generated pictures are displayed on a television screen with the same views as if the investigator had actually removed the tissue from the body and sliced it open to study its internal organs.

"The computer system allows the investigator to obtain images of selected structures inside the body from any angle of view," explains biocomputer scientist Dr. Richard Robb, another member of the Biodynamics Research Unit. "In effect, the body is thinly sliced mathematically in any direction by the computer so that its internal structure can be studied in detail. The computer converts standard x-ray views--rapidly produced by the system--to numerical forms and then reconstructs from these values those particular views most helpful in determining the exact location and extent of areas under study."

Federal grants from the Division of Research Resources (DRR) funded the computer facility and the National Heart, Lung and Blood Institute (NHLBI), funded the DSR scanner and the research programs which utilize the DSR for investigative studies.

In addition to the NIH grant, support was given by the American Heart Association, the Ripple Foundation of New Jersey and other private sources.

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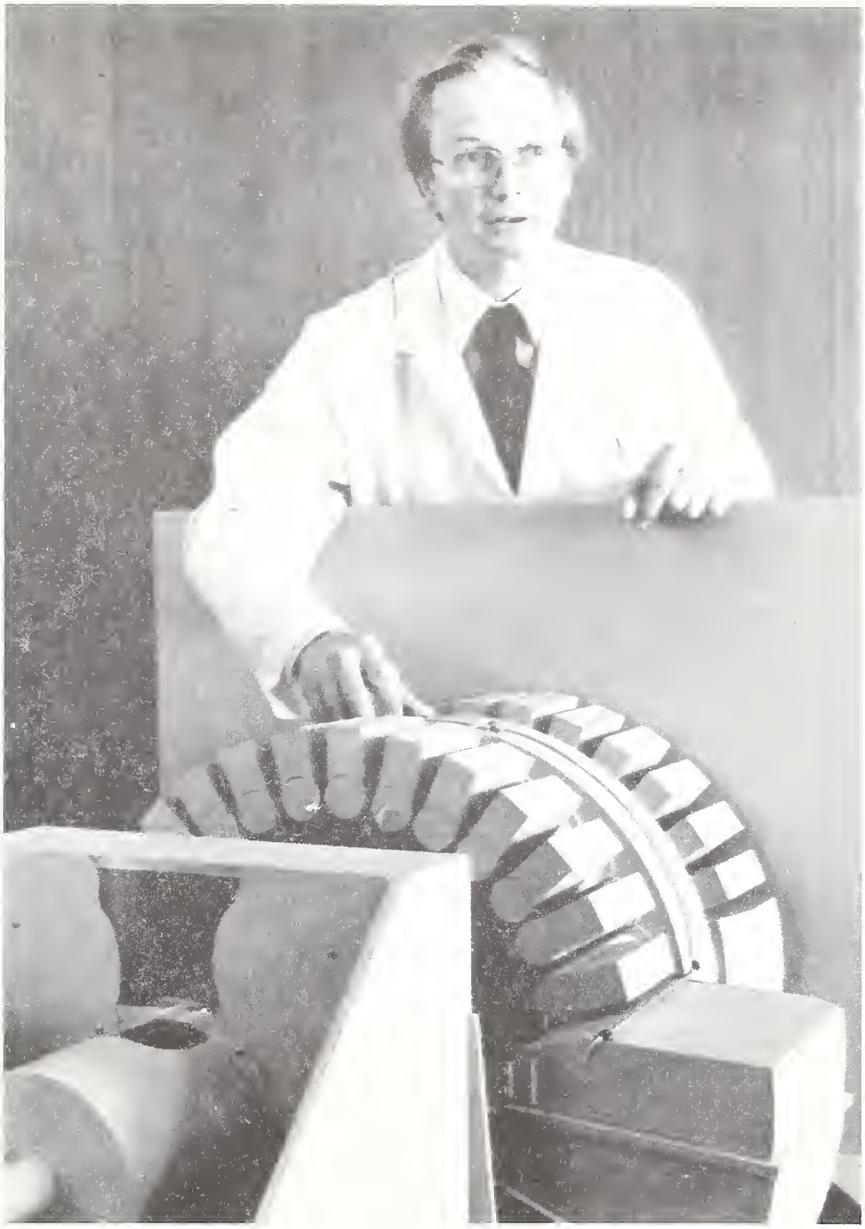

Physiologist Erik Ritman explains a model of the DSR computer-based system that will help benefit cardiovascular research. (NIH Photo #1648)

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Dr. Richard Robb, biocomputer scientist at Mayo Clinic, works with the computer that translates the DSR x-rays into three-dimensional video photos of the heart, lungs and large vessels. (NIH Photo ***#1649****)*

###

ROUND-THE-CLOCK OXYGEN FAVORED OVER HALF-DAY THERAPY FOR SEVERE LUNG DISEASES

By York Onnen

Despite preliminary evidence to the contrary, 12-hour nighttime oxygen therapy is not as beneficial as round-the-clock oxygen therapy in extending the life of patients with severe respiratory impairment. This finding was the result of a collaborative study initiated in 1977 by the National Heart, Lung and Blood Institute.

The study, conducted at six medical centers on 203 volunteers, compared the effects of 12-hour nighttime and round-the-clock oxygen therapy. All the patients suffered from chronic obstructive lung disease at a stage where the lung could no longer supply the body with enough oxygen to meet its metabolic requirements. Between 250,000 and 500,000 Americans require oxygen treatment for this stage of chronic lung impairment which almost always leads to death.

Preliminary evidence from earlier investigations had indicated that when oxygen was administered for only 12 hours nocturnally (instead of continuously for 24 hours), it seemed to prevent such complications of oxygen deficiency as an increase in the number of circulating red blood cells and elevated pressures in the pulmonary artery. Since continuous therapy is both costly and inconvenient for ambulatory patients, and because oxygen deficiency is especially severe during sleep, 12-hour oxygen therapy would be a feasible alternative if it could be as effective as continuous therapy.

The study was designed to compare 12-hour nocturnal and 24-hour oxygen therapy not only with regard to death, but also for effects on physiologic and neuropsychologic functions that affect the quality of a patient's life.

The patients who agreed to participate in the study were randomly assigned to either the continuous or the nocturnal oxygen therapy program. After all patients had been followed for at least twelve months the death rate was

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11.9 percent in the group receiving continuous oxygen therapy, and 20.6 percent in the group receiving only nocturnal oxygen. For patients followed for 2 years, principally those who joined the study at the beginning, mortality was 22.4 percent and 40.2 percent, respectively. By the end of the study, 31.5 percent of the participants had died.

Dr. Claude Lenfant, the director of the Division of Lung Diseases, said: "The results of this clinical trial indicate that the number of deaths is twice as great among patients in nocturnal oxygen therapy as among those in continuous therapy. While nocturnal oxygen therapy may be less expensive, it is not as effective in extending life in patients with this particular lung disease."

In aspects of the study other than the number of deaths, Dr. Lenfant said: "The differences are less clear. There is evidence that patients with the severest respiratory impairment benefited most from the continuous oxygen therapy. Although not all data from the study have as yet been analyzed, it is anticipated that it will contribute considerably to our understanding of the ultimate role oxygen therapy may have in the treatment of lung diseases. For example, there are indications that oxygen therapy may slightly improve neuropsychologic conditions and the patient's perception of his or her quality of life. These indications, however, need further verification."

The results of the trial are reported in the Sept. 3 issue of the *Annals of Internal Medicine* under the title "Continuous or Nocturnal Oxygen Therapy in Hypoxemic Chronic Obstructive Lung Diseases: A Clinical Trial." The centers participating in the trial were: Henry Ford Hospital, Detroit; Northwestern University, Chicago; the University of Manitoba, Winnipeg; the University of California and the Scripps Clinic Research Foundation, San Diego; the University of Colorado, Denver; and, the University of Southern California, Los Angeles.

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PROLONGED SURVIVAL OF PANCREATIC TRANSPLANTS IN MICE MAY LEAD TO BETTER TREATMENT OF DIABETES

By Patricia Sheridan

A significant advance in the search for better methods of treating diabetes has been reported by scientists supported in part by the National Institute of Arthritis, Metabolism and Digestive Diseases (NIAMDD).

In the July 11, 1980 issue of *Science*, Dr. Paul Lacy and colleagues at the Washington University School of Medicine describe a procedure for successfully transplanting islets, clusters of insulin-producing cells, from one animal species to another. Furthermore, they have shown that the transplants, taken from healthy rats, could reverse diabetes in the diabetic mice that received the transplants.

Insulin-dependent diabetes mellitus, the most severe form of diabetes, affects approximately 300,000 Americans. The disorder occurs when the beta cells in the pancreas degenerate, producing little or no insulin. Lacking the ability to secrete natural insulin, persons with this form of the disease must take daily injections of this hormone to regulate the body's use of glucose for energy or storage.

This method of treating diabetes, however, has not been entirely satisfactory, since daily insulin injections do not mimic the natural action of normal beta cells in achieving precise minute-to-minute control of blood glucose and other metabolic processes. Many scientists believe that lack of good blood sugar control results in the chronic complications of diabetes which affect the eyes, kidneys, heart and nervous system. Successful transplantation of healthy insulin-producing islets that restore precise blood sugar control could possibly prevent, arrest or reverse these life-threatening complications.

In recent years, islet cells and whole pancreas glands have been transplanted successfully into inbred strains of diabetic animals. Islet cell trans-

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plantation in experimental animals of different strains, however, has been impeded by the problem of immune rejection, a natural response by which the body recognizes transplanted tissue as a foreign substance and destroys it.

Significant progress was made last year when Dr. Lacy, Mallinckrodt Professor and chairman of the department of pathology, in collaboration with Drs. Joseph M. Davie and Edward Finke, transplanted rat islet cells into rats of a different genetic strain without graft rejection. (*Science* Vol. 204, pp. 312-3, 1979). This successful transplant laid the groundwork for the research team's most recent accomplishment in transplanting insulin-producing islets from rat to mouse without rejection.

In this project, healthy rat islets were placed in tissue culture for seven days at 24° C to lessen the chances of rejection by the immunologically active cells present in the islet tissue. Immediately before transplantation, the diabetic mice received a single injection of immune-suppressing drugs to minimize their natural immune response and to reduce further the risk of graft rejection.

The rat islets were transplanted into the livers of 10 diabetic mice. Within two to four days, the elevated blood glucose levels of the mice returned to normal. Most significantly, seven of the 10 mice continued to maintain normal blood glucose levels 116 days after transplantation.

These animals will remain under close observation to determine whether rejection of the islet cells will occur at a later time, or whether this procedure has, in fact, produced indefinite graft survival. In contrast, diabetic mice receiving transplants of untreated rat islets without the immune-suppressing injection rejected their grafts within 7-12 days.

The ultimate goal of the research team is to determine whether the simple combination of islet incubation at low temperature and a single immune-suppres-

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sing injection will eventually permit successful transplants in human diabetics. While the results reported by Dr. Lacy and his associates represent a significant scientific advance, their application to the treatment of diabetes in man is not yet feasible.

Several major obstacles must be overcome before this type of islet transplantation can be attempted in humans. For example, adaptability of the culture procedure must be examined as well as the specific cell types and numbers responsible for cell rejection.

Further research is also required to determine whether islet transplants into different species will maintain normal metabolic activity in recipients for extended periods of time. Similarly, it will be important to determine the best site for implantation as well as the minimum number of transplanted islet cells required to normalize blood glucose levels.

If adequate supplies of animal islets can be maintained and stored, their use in human transplantation could remedy the present scarcity of human tissue.

Through continued research, it may be possible to use islet transplants for treating diabetes in man and to assess the relationship of normalized blood glucose control on the development, prevention or arrest of the chronic complications of diabetes.

###

EXPERIMENTAL ANTIVIRALS OFFER HOPE IN CONTROLLING VIRAL INFECTIONS

By Mary Donovan

The continuing development of antiviral substances has been a remarkable achievement in the fight against viral infections. Since this era began nearly two decades ago, there have never been so many experimental antivirals showing promise as effective agents against many of the serious viral diseases as there are today.

Several of these drugs have been made synthetically and are used to fight viruses at specific sites, while others such as interferon, were discovered as natural substances produced in the body that have the capacity to fight infections.

The Antiviral Substances Program of the National Institute of Allergy and Infectious Diseases (NIAID) supports clinical trials to test the effectiveness of many of these substances. The following is a thumbnail sketch of some of the more promising antivirals currently under study.

Ara-A: Adenine arabinoside is the first agent to be licensed in the United States for systemic treatment of serious virus infections, such as herpes simplex (fever blisters, cold sores), varicella (chickenpox), cytomegalovirus (salivary gland virus), and vaccinia viruses (smallpox).

In 1977, clinical trials demonstrated that treatment with ara-A significantly reduced the number of deaths caused by biopsy-proven herpes encephalitis, a rare and often fatal inflammation of the brain. Recent studies involving 56 newborns with systemic herpes simplex infections have shown that the overall death rate was also drastically reduced. Currently, two trials are in progress to evaluate the effectiveness of ara-A in treating patients with varicella-zoster (chickenpox, shingles), and mucocutaneous herpes (herpes of the mouth). The results are expected to be completed by the end of this year.

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As a topical preparation, ara-A has not been effective in treating mucocutaneous genital herpes, probably because of its limited solubility. A more soluble form of the drug, adenine arabinoside monophosphate (ara-AMP), has been developed and is under investigation for the treatment of herpes encephalitis and chronic hepatitis B infection. Eventually, this newer derivative of ara-A will be tested for its effectiveness in treating newborns with herpes.

Interferon: Although interferon has received much publicity as a potential antitumor drug, its usefulness as an antiviral agent has been more clearly demonstrated. In studies with nearly 150 immunocompromised patients, interferon reduced the pain and spread of lesions caused by herpes zoster and lowered the risk of complications. Interferon is also being evaluated for its effectiveness in preventing herpes varicella in children suffering from leukemia.

In other studies, interferon has prevented the recurrence of herpes lesions in patients undergoing surgery for trigeminal neuralgia, a painful condition affecting facial nerves.

A small percentage of patients with acute hepatitis B infection become chronically infected and are therefore capable of transmitting the infection as well as developing further liver damage. Results were encouraging when 38 patients with chronic hepatitis B infection were treated with a combination of interferon and adenine arabinoside (ara-A), followed by a maintenance program of interferon for several months.

Premenopausal women seem to be the best candidates for this type of therapy. Most hepatitis B carriers are men, so subsequent studies will focus on developing regimens that will be effective in men as well as in women. Additional combination drug trials will be conducted to evaluate the role of other experimental antivirals as possible substitutes for ara-A.

Interferon's effectiveness in preventing and treating the common cold or

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upper respiratory viral infections is however, more controversial. Currently, a clinical study is underway to determine whether patients given a double dose of interferon before exposure to rhinovirus (common cold viruses), is more effective than patients receiving two doses of interferon after exposure to rhinovirus.

Acyclovir: Developed by Burroughs-Wellcome Laboratories, acyclovir (ACV) is one of the most promising new antiviral substances used specifically for herpes virus infections. This compound has been found to have significant antiviral activity and few side effects in infected animals. Clinical trials are currently underway using ACV topically in the treatment of herpes labialis (fever blisters, cold sores) and genital herpes, and, to date, have produced encouraging results. Future clinical studies will compare ACV and ara-AMP for the treatment of biopsy-proven herpes encephalitis.

Amantadine: Although amantadine was licensed for the prevention of influenza A in this country as early as 1966, it was not widely accepted, due to a variety of factors. Since then, a number of studies have been performed to investigate the safety and efficacy of this drug. During an outbreak of flu in 1978-9, college students were given amantadine to prevent influenza infection. Results showed that amantadine was effective in reducing the duration and severity of symptoms. A more recent study compared amantadine and rimantadine, a derivative of amantadine, found both drugs to be effective. However, amantadine exerted a more rapid effect and was chosen to be the drug of choice by the investigators. In the future, studies will continue on the relative merits of both drugs.

In addition to the antiviral drugs mentioned, other substances such as ribavirin, phosphonoacetic acid, phosphonoformic acid, bromovinyl deoxyuridine, arildone and 2-Deoxy-D-glucose are being studied in the treatment of viral

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infections. Some of these substances appear to have therapeutic potential, but it is too early to predict the extent of their usefulness in clinical practice.

The next few years should be exciting ones, yielding many more clinically useful agents for the prevention and treatment of viral disease.

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News&Features
FROM NIH

NEW TEST MAY HELP IDENTIFY FOODS CAUSING TOOTH DECAY

By Marian Segal

A team of scientists at the National Institute of Dental Research has designed a new test to measure the decay-causing potential of specific foods. A description of the method and results from the first foods tested with it appeared in a recent issue of the *Journal of the American Dental Association*.

The new screening method, developed by Dr. William Bowen and his colleagues in the National Caries Program, ensures reliable results because only the foods actually being tested come into contact with the teeth of the study animals (rats). The rats receive other foods also for essential nutrients, but these are fed to them by a stomach tube twice a day.

Normally, rats eat many times a day and may be choosy about how often and how much they eat. To ensure that all the foods are ingested with equal frequency, an automatic feeding machine releases the test food to the animals 17 times a day. Any decay that develops comes from the interaction between the test food and the microbes on the animals' teeth and cannot be ascribed, for example, to differences in frequency of eating. To assure that decay-causing microbes are in all rat mouths, the animals are deliberately infected with *Streptococcus mutans*, the chief bacterial suspect in human tooth decay.

The cariogenic (decay-causing) potential of 11 representative food products was tested. The highest rates of decay resulted from cream-filled chocolate cookies, several breakfast cereals containing 8-60 percent sucrose (table sugar), and sugar-coated chocolate candies. Foods that tested somewhat lower in cariogenic potential were potato chips, caramels, chocolate bars, a cereal with 2 percent sucrose and plain starch.

The test results showed that, although all foods containing sugar were to some degree cariogenic, sugar concentration alone did not determine the degree

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of cariogenicity. Other ingredients added to foods can influence their cariogenicity by either retarding or enhancing the effect of sugars. For instance, sugar supplemented with dicalcium phosphate was less cariogenic than sugar alone. Dicalcium phosphate may be added to some foods to improve consistency or to buffer tartness. The frequency of eating sugar, rather than simply the amount consumed, also influences bacterial growth.

Researchers have known for years that tooth decay is caused by the interaction of three factors. First, the tooth must be susceptible to decay. Second, decay-causing bacteria must be present in the mouth, and third, the diet must promote bacterial reactions that cause tooth decay. Despite this knowledge, scientists have found it hard to assess quickly the relationship of particular foods to decay because the decay process occurs intermittently over a long period of time. Additional problems arise because test foods had to be mixed with essential nutrients and the frequency of eating was uncontrolled.

The new test carefully controls what foods are in contact with the teeth and how many times during the day. Furthermore, the test is relatively speedy--it takes about two months from the beginning of the experiment until the results are apparent and analyzed.

"The technique is quick, reproducible, and will permit foods to be ranked for cariogenic potential," said Dr. Bowen.

"Researchers, regulatory agencies, food manufacturers and consumers can gain information from extensive use of these tests on which foods pose the greatest hazards to the teeth. These foods can then be avoided or considered for reformulation to reduce or eliminate their cariogenic hazard."

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News&Features
FROM NIH

LONGER LIFE FOR MANY CANCER PATIENTS PROMOTES INTEREST IN INFERTILITY CAUSED BY DRUGS

By Susan Johnson

The increased life expectancy of many cancer patients resulting from advances in chemotherapy has sparked interest in how these powerful drugs affect the patients' ability to have children. Studies at NIH and other research centers have shown that long-term infertility is a common side effect of cancer chemotherapy.

The recent finding by the National Cancer Institute that Hodgkin's disease, a once-fatal cancer, can be cured with a combination of drugs underscores the importance of research in this area.

About half of the approximately 7,000 Americans stricken by Hodgkin's disease each year are young adults, primarily men. Studies conducted jointly by the National Institute of Child Health and Human Development and NCI have shown that the drug combination responsible for the cure causes sterility in 95 percent of men and about 50 percent of women treated. The drug-induced infertility has persisted in patients followed for as long as 12 years.

Men are more susceptible to gonadal damage from chemotherapy than are women because cell division is more frequent in the testes than in the ovaries, explains Dr. Richard Sherins, an infertility specialist in the Developmental Endocrinology Branch, NICHD. Anticancer drugs inhibit rapid cell division, and therefore have a greater impact on the testes.

In men, the drugs used to treat Hodgkin's disease destroy the cells which give rise to sperm. In women, scientists believe, they destroy a certain number of eggs in the ovaries.

As a result, women over 35 often become sterile after treatment, while women under 35 usually continue to ovulate. Younger women have more eggs than older women, so their supply is not depleted as readily. At least 10

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more years of followup are needed to determine if the younger women treated with chemotherapy will experience early menopause.

Some NIH studies have shown that the testes of adolescent boys are highly sensitive to the drugs used to treat Hodgkin's disease. Sperm production ceases after treatment, and production of testosterone, the hormone responsible for secondary sex characteristics in the male, decreases.

The NIH studies suggest that prepubertal boys show no evidence of damage to the testes caused by these drugs, but follow-up of the boys into adulthood will be necessary to determine whether their testicular function remains normal. The effect of the drugs on the ovaries of adolescent girls is still unknown.

Not all anticancer drugs are as harmful to reproduction as those used to treat Hodgkin's disease. A nearly completed study by NICHD and NCI indicates that the combination of drugs frequently used to treat acute leukemia has little effect on the testes of adolescent boys. An earlier study by the two institutes showed that the ovaries of most adolescent girls who receive chemotherapy for acute leukemia develop normally.

The drug combination used to treat another cancer, soft tissue sarcoma, usually causes transient sterility in men and women under 40 and long-lasting infertility in patients over 40. This finding resulted from studies conducted by Dr. Sherins, NICHD and Drs. Robert Shamberger and Steven Rosenberg, NCI. In addition, patients who receive radiation near the testes or ovaries while taking the drugs suffer long-term sterility regardless of age.

The effect of chemotherapy on reproduction depends on the class of drugs used and the dosage given, not on the disease being treated, says Dr. Sherins.

The drug combinations given to patients with Hodgkin's disease and soft tissue sarcoma contain alkylating agents, a class of drugs known to damage the testes and ovaries. Another class of drugs known to cause gonadal injury, the

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methylhydrazines, is also included in the Hodgkin's combination. Chemotherapy for acute leukemia patients includes neither class of drugs.

Preservation of semen collected before treatment offers hope for some men who wish to father children following cancer chemotherapy, but it cannot help most patients, says Dr. Sherins. The process of freezing and thawing semen decreases the quality of sperm. Even with preserved semen from healthy men, the chance of conception is only about 50 percent. The sperm of men with serious tumors is often of poor quality to begin with, thus further lowering the chance of preserving viable sperm.

Many questions about the effect of anticancer drugs on fertility remain unanswered, Dr. Sherins says. While the impact of some drugs, such as the alkylating agents, has been defined, the effects of other commonly used anticancer drugs are not known. Further studies are needed to determine which drugs can cause infertility, at what doses, and how long the drug-induced sterility will last.

Also unclear, he says, is the role that age plays in susceptibility to gonadal damage from anticancer drugs. For example, scientists do not know why men over 40 suffer more damage to the testes from chemotherapy for soft tissue sarcoma than do younger men.

One concern of patients who remain fertile or regain their fertility following chemotherapy is whether their future offspring will have an increased risk of birth defects. So far, says Dr. Sherins, the risk of genetic damage to sperm and egg cells from anticancer drugs is unknown. A few experimental studies have shown that the offspring of rats treated with alkylating agents have no increased incidence of genetic damage.

At the present time, infertility must be considered an unavoidable side effect of some anticancer drugs, concludes Dr. Sherins.

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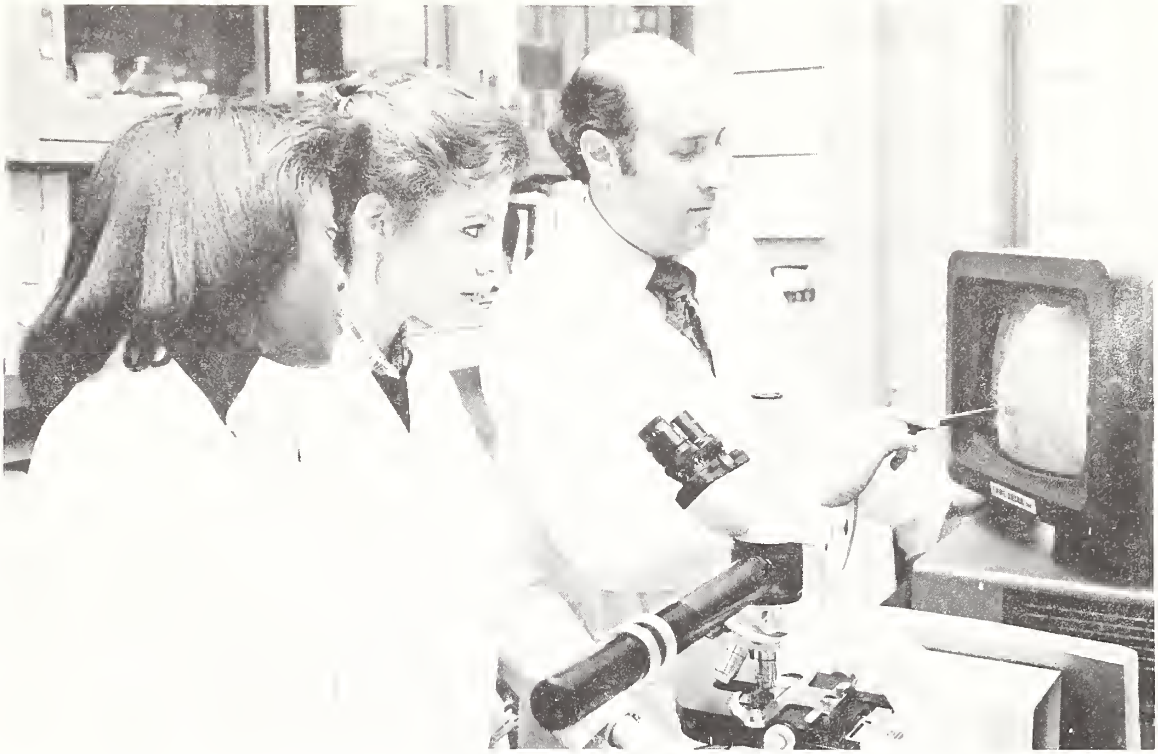

Dr. Sherins (r) and assistants Natasha Norman (1) and Amy Patterson (c) examine tissue taken from the testis of a patient being treated for Hodgkin's disease. (NIH Photo #1650)

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HUNTINGTON'S DISEASE TO BE STUDIED IN "CENTERS WITHOUT WALLS" A NEW APPROACH TO NEUROLOGICAL RESEARCH

By Sylvia Shaffer

Two innovative research centers to study Huntington's disease, whose most famous victim was folksinger Woody Guthrie, have been established with a $5 million award from the National Institute of Neurological and Communicative Disorders and Stroke. Other neurological disorders characterized by brain degeneration and abnormal body movements will also be investigated.

The grants were made to Johns Hopkins University School of Medicine in Baltimore and to a consortium of medical institutions in Boston, headed by Harvard University Medical School.

Each grantee will establish a "Center Without Walls", a new approach to research on serious but little understood disorders of the nervous system.

Unlike the traditional idea of a specialized disease center consolidated under one roof, Centers Without Walls will not emphasize a central location for research. Instead, a Center Without Walls consists of investigators engaged in basic or clinical research in different departments within a university, or at different universities and medical centers. Patients and their families may be seen in clinical research facilities in any of the institutions comprising the center.

The centers will be focal points for research into many devastating brain disorders. One important goal will be to identify large numbers of patients with long-term neurological diseases so that the social, economic, psychological and legal problems these patients and their families face can be dealt with more effectively.

In Boston, a five-year award of $3,307,026 for direct costs will support investigators in various departments within Massachusetts General Hospital, McLean Hospital, Boston University, Tufts New England Medical School, the Boston

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Veterans Administration Hospital and the University of Massachusetts.

This Center Without Walls will support 10 scientific investigations, including several projects to map and measure levels of brain hormones and neuropeptides--brain chemicals that influence thinking, emotions and pain perception.

Other investigations focus on developing better methods for analyzing brain tissue to detect changes characteristic of degenerative brain disorders like Huntington's disease and Alzheimer's disease.

As part of the center's studies, a team of molecular geneticists at Massachusetts General Hospital will use recombinant DNA techniques to try to identify the exact location of the abnormal gene that causes Huntington's disease. Such "gene mapping" research may lead to breakthroughs in preventing or treating genetic disorders.

Dr. Joseph B. Martin of Massachusetts General Hospital, a Harvard affiliate, is the center's director.

The Johns Hopkins University will receive $1,837,385 to cover direct costs of a center to be directed by Dr. Marshal F. Folstein. The center will oversee nine research projects, including efforts to identify and examine all Huntington's disease patients in Maryland and to support research in genetic counseling techniques. The Johns Hopkins group will investigate abnormal eye movements and swallowing difficulties in Huntington's disease patients. They will also study the effects of lesions in the basal ganglia, an area of the brain known to be involved in Huntington's disease, Parkinson's disease, Tourette syndrome and other movement disorders.

This center will involve several departments and programs within the university, including psychiatry, neurology, genetics, epidemiology and public health. Patients will enter the center's programs through the J. Earle Moore Medical

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Genetics Clinic at Johns Hopkins.

Establishing Centers Without Walls fulfills one of the major recommendations of the Commission for the Control of Huntington's Disease and Its Consequences. The commission reported its findings to Congress and to the president in October 1977.

Scientists at the National Institute of Neurological and Communicative Disorders and Stroke estimate that more than 50 million Americans suffer from some kind of brain or nervous system disorder. Huntington's disease, a hereditary disorder marked by progressive loss of mental faculties and uncontrollable movements, afflicts at least 20,000 people in the United States, with some 40,000 at risk of having inherited the defective gene.

Many investigators see Huntington's disease as a model for other crippling and lethal neurological disorders.

"We are enthusiastic about the Centers Without Walls," said Dr. Donald B. Tower, NINCDS director. "They will attract patients from a much larger geographical region than is usually served by a single medical center, and this will give the investigators a much larger patient population than they usually see."

"The investigators in these centers will be breaking new ground in brain chemistry, genetics and health care research while looking for answers to basic questions about the human brain."

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At Johns Hopkins, Dr. Susan Folstein examines Mrs. Dwaine Cowan, for hand and arm tremors. (NIH Photo #1651)

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News & Features
FROM NIH

BONE MARROW TRANSPLANT CORRECTS FATAL BONE DISEASE IN INFANT

By Wendy Zellner

A successful bone marrow transplantation appears to have corrected a rare and usually fatal bone disorder, osteopetrosis, in a 5-month-old infant, according to a research team supported by the National Institutes of Health.

The female infant has developed normally since receiving the transplant in 1978 from her 5-year-old brother who had identical HLA antigens. HLA antigens are genetic markers of the body's immune system, and therefore, are important in cross-matching for transplantation procedures. The infant is now 2 1/2 years old and shows no signs of the disease.

Osteopetrosis, also known as Albers-Schonberg syndrome, or marble bone disease, is an inherited disorder, characterized by dense, fragile bones whose tissue invades the bone marrow cavities. The benign or "adult" form is associated with minimal disability and patients may enjoy a normal life expectancy. However, the "infantile" or malignant form is usually fatal.

In its infantile form, osteopetrosis can cause facial paralysis, enlarged liver and spleen, frequent fractures and blood abnormalities. Blindness and deafness are also common and many victims die before reaching adulthood. Until now there has been no effective long-term therapy for the disease.

From previous studies in animals, bone marrow transplantation was found to correct osteopetrosis after the diseased animals have received massive doses of radiation. In the reported study, the infant was treated before transplantation with immunosuppressive drugs and total-body irradiation to decrease the chances of graft rejection.

To minimize the side effects of the radiation, doctors used a low dose and protected the child's head and lungs with lead shields. Marrow obtained from her brother's hip bones was then transmitted intravenously to her.

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Seven weeks after the transplant, normal bone growth was found and marrow biopsies revealed that her marrow cavities were enlarging due to increased bone resorption. Within 12 weeks of the transplantation, the infant's blood and biochemical abnormalities were completely corrected. The baby's vision, hearing, growth and development were still improving more than a year after the procedure.

The infant never experienced graft rejection or graft-versus-host-disease, a reaction in which the donor's cells attack the tissues of the transplant recipient. Researchers credited her young age, the total body irradiation, and compatibility between the infant's bone marrow and her brother's bone marrow with contributing to the infant's rapid and complete response to treatment.

In the past, the small number of transplants in patients had not been as encouraging. Either graft-resistance or the fact that these patients did not receive immunosuppressive drugs before the transplant may have led to only partial recovery.

Osteopetrosis is an imbalance between the body's continuous processes of bone formation and resorption. This imbalance results from decreased function of the osteoclasts, the bone-forming cells responsible for resorbing bone and calcified cartilage.

Osteoclasts are thought to be derived from bone marrow and spleen cells. Convincing evidence for this came from studies by Dr. Donald Walker and his colleagues at Johns Hopkins University. Under a grant from the National Institute of Arthritis, Metabolism and Digestive Diseases, they discovered that osteopetrotic rodents recovered when the circulatory systems of normal mice and their diseased littermates were surgically connected.

It was also learned that osteopetrotic mice regained their ability to resorb bone even after short exposures to normal circulation. In addition, bone resorption continued to occur three to six weeks after the cross-circulation had been

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severed.

Scientists explained this improvement in bone resorption by the "stem cell hypothesis." It is believed that stem cells (immature cells) originating from the bone marrow and spleens of the normal mice entered the circulation and migrated to the active growth centers of the skeleton. There, these migratory cells left the blood stream and new normal osteoclasts and other bone marrow derivatives emerged.

Investigators discovered that the recovery rate was dependent upon the animal's age at time of treatment. When osteopetrotic mice were connected to normal littermates at 10 days of age, they recovered within one month. When the diseased mice were connected at six weeks of age, recovery required at least eight weeks.

The results of this study led researchers to believe that use of bone marrow transplants in mice could then be applied clinically to the treatment of osteopetrosis in humans. Cell infusions were prepared from either the spleen or bone marrow of normal mice. Then cells were infused intravenously into osteopetrotic littermates that had received sublethal doses of radiation. This procedure restored normal bone resorption in diseased mice as early as two weeks after transplantation. However, only those mice that had been irradiated before transplantation recovered.

Furthermore, when this experiment was performed, researchers were able to induce osteopetrosis in normal mice given cell infusions from diseased littermates. Calcified cartilage and excessive bone accumulation appeared within a few weeks after transplantation demonstrating that osteoclasts were not functioning normally.

Recently a full report of the successful transplant in the 5-month-old was published by Dr. Peter F. Coccia, associate professor of Pediatrics at Rainbow

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Babies and Childrens Hospital in Cleveland, and his colleagues at Washington University in St. Louis, Mo., in the *New England Journal of Medicine*. This research was supported by the National Institute of Arthritis, Metabolism and Digestive Diseases, the National Heart, Lung, and Blood Institute, the National Cancer Institute and the National Institute of Dental Research, components of the National Institutes of Health, Bethesda, Md.

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